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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JULY 1940

HEART DISEASE—A WORLD PROBLEM*

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SOLOMON said, "Keep thy heart with all diligence; for out of it are the issues of life" (Prov. 4:23). Those were the days when the heart was the seat of the soul, the badge of bravery, and the abiding place of affection. Far be it from me to assume that the physical heart can rank with such attributes in world history, particularly in the troubled times of today. To paraphrase the scriptures, "For what is a man profited if he shall keep his heart whole and lose his own soul? or what shall a man give in exchange for his soul?" Fortunately in our mission as physicians we are not limited to the mere technical work of diagnosis and impersonal treatment; it is our privilege to dispense courage, sympathy, and an attitude of mind which in themselves fortify our drugs, our diets, and our bloodletting.

In 1618, ten years before Harvey, Albertini wrote a book on the heart, not only the first one on that organ as such, but actually entitled *Affections of the Heart*. Unfortunately the book does not live up to the title except in one particular. He discusses at great length the one chief symptom that was at that time accredited to the heart, namely palpitation, as had been done by many others before him, especially by Galen

* The Hermann M. Biggs Lecture, given April 4, 1940, at The New York Academy of Medicine.

and Avicenna; he mentions the fact that all sorts of things can excite the heart to palpitate, both cardiac and noncardiac, that is, that much palpitation occurs without heart disease, which at that time in history was just beginning to be clearly recognized as possible without an early death.

But it is Senac whom I would like to quote in particular, to establish a background for the broad cardiological viewpoint of today. Senac was the first important clinical worker in the field and his writings in 1749 stand out as the pioneer textbook on heart disease based on the physiological and anatomical contributions of Harvey, Lower, and Mayow, and on the reports of cardiac pathology by Bonetus, Vieussens, and Lancisi, during the century that preceded him. There are three points stressed by Senac in the preface of his book two hundred years ago that I would like to stress today as an introduction to the subject of heart disease as a world problem: First, on page xiv, he writes, "The mind is not great enough and life is too short to embrace all anatomy. In spite of all the help of our predecessors it is hardly possible for one man to develop exact knowledge of a single viscus. Those long works which enclose the details of every part of the body announce their own sterility, even by their very extent. They are like maps of the entire world where whole kingdoms appear as dots."

Second, on page xvii, Senac states, "In citing authors I have tried to avoid the national prejudice which dominates even savants. Several imagine that genius and knowledge are attached to their particular country and that the other nations are condemned by nature to sterility. This vanity can be useful to the states; by inspiring confidence and scorn, it inspires courage or rather ferocity, but it degrades the mind. Genius is the property of no nation; it is mingled by chance with stupidity and ignorance. . . . Let those who have the spark be separated by the seas or by the long stretches of the earth, they form a republic whence the rest of mankind is excluded."

And finally, on pages xl and xli, "The heart is a kind of center where all disorders converge. All the ills of the rest of the body reflect on this organ. As soon as some part is irritated or inflamed, the heart may partake of its suffering. . . .

"What are the obstacles against which the heart rises up and rebels, so to speak? Is it some obstruction or a thickening of the blood, irritation, plenitude, or quality of the body fluids? How do such causes,

sometimes so far removed from this organ, trouble its action? . . . We often multiply without reason the sources of our ills; without suspecting the true causes, we give the others added importance.

"We know hardly how we live, but we know still less how we die; what is the cause which stops the heart when a fever leaves no trace of its ravages? . . . One must then seek the causes of death in the outside influences which arrest the movement of the heart, so fragile a bond between soul and body.

"But the heart itself is exposed to various maladies. Observation and experiment are guides which lead us to the source of these ills. The descriptions recorded in many works are too diffuse, and so it has been necessary to separate the factors and to follow them right to the very causes discovered by dissection, to study them, to note their differences, and to relate them to the structure and the action of the organs. . . . The present volume will include therefore a detailed account of the derangements of the heart, which organ is no less limited in the number of causes which trouble its action than in the varieties of this very action itself." . . . Senac ends this very intelligent preface by quoting an ancient author, "Our works are not such as we desire but such as they can be; minds more enlightened than ours will add what has escaped us."

The chief reason why I have quoted Senac at some length is to point out that he had at least the vision of the importance of the diagnosis of heart disease according to cause; structural changes and disturbed action he recognized as secondary to such underlying causes, which, at that time, were very obscure and even today are largely unsolved although they are far clearer as problems to be unravelled. Thus, Senac may rightly be called the pioneer in the modern three-fold diagnosis of heart disease according to etiology, structure, and function.

But before we go further it will be well to pause a moment to state what I mean by the term heart disease. There is a difference of opinion now, as in all ages, about the meaning of the word "disease" itself. Literally dis-ease is discomfort and the word discomfort may be applied to a slight and transient headache the "morning after"; to a little gas in the stomach after swallowing fluids too rapidly; or even to a knock on the crazy bone, or a single extrasystole. It would seem far fetched, however, to call these things disease as we ordinarily use that term. Moreover, Webster's International Dictionary labels as obsolete the definition of disease as discomfort. Even if we grant that the definition of

heart disease as used medically may have a wide range of meaning from the slightest possible and least important transient disorder of function like an extrasystole to the most extensive lesion of the heart compatible with life, we shall only confuse the issue of our present consideration of heart disease as a world problem if we include two particular groups of cases. Like the poor they are always with us and always will be; they comprise practically the sum total of mankind and do not have any important bearing on really significant heart disease. These two groups of cases are in the first place all those who at one time or another have a few cardiac symptoms of neurocirculatory asthenia or a premature beat or two, and in the second place, all those who have very slight changes in the myocardium secondary to a thousand and one diseases which may or may not be fatal in themselves, the myocardial changes such as terminal cloudy swelling having no material bearing on the course or outcome of the disease.

On the other hand, there enter for our present consideration certain well recognized and common kinds of heart disease, such as the rheumatic; a few rarer or more obscure types, such as neoplasm; and occasional effects from various miscellaneous conditions, such as anemia and malnutrition, which when severe can appreciably affect the heart but which in ordinary degree do not cause uncomplicated heart disease.

I cannot sufficiently stress the importance of the etiological point of view about heart disease. It is an old story for some of us brought up under the medical influence of Richard Cabot in Boston or of John Wyckoff and Alfred Cohn in New York, and it fits into the conception of preventive medicine championed so strongly and effectively by the pioneer for whom this lectureship was named, Hermann Biggs of New York City, but it still remains a novel point of view in some parts of the world and even in our own tables of mortality statistics where it should be properly established. There is still talk of cardiac enlargement and failure, of valvular disease and arhythmias, and of chronic myocarditis as the chief interests of the doctor in his study and care of patients with heart trouble, be he family physician or specialist. This is to liken the function of the medical man to that of the salvage squad after the fire fighters have left—an essential job to be sure but not the vitally important task of the early recognition, and treatment, and prevention of the underlying causes of heart disease. The cardiologist like other members of the medical profession should strive to wipe out the

need of his services; he probably will not be able to do so entirely for it seems likely that the aged will still suffer and succumb to heart disease for generations at least after other mortal ills have been conquered, though even that need not be considered forever insuperable.

It is the family doctor who should be the first to discover the beginnings of disease which may carry heart trouble in its wake and it is he who may also find the actual beginnings of heart disease itself. He should not wait to act till he is confronted by heart failure; he should discover the high blood pressure or the valvular disease or the cardiac enlargement long before failure comes. He may need to call in the specialist for help but his most useful service will be in the attempt to study all the circumstances of the very onset of the causes of the underlying disease and not so much of the resulting heart disease. Anyone with his eyes open may discover important clues, and the important clues in the campaign for the prevention of heart disease are in the very beginnings of the causes of heart disease.

One of the most important points I can make in my discussion this evening is, that in order to shift the emphasis from heart disease to its causes where it rightfully belongs, we should record as the chief diagnosis the causative factor first, and second, the presence or absence of any resulting heart disease, and finally, the degree of heart trouble if present. Thus, instead of diagnosing hypertensive heart disease it is more to the point to diagnose hypertension with or without cardiac enlargement or failure, just as we would diagnose hypertension with encephalopathy or with nephritis or renal failure.

Heart disease is a world problem, as much as is tuberculosis or dysentery or influenza, but it has not yet been investigated as such, in contrast to many of the infectious diseases which have scourged the world, especially in the form of waves of devastating epidemics. It is natural that the rapidly fatal and highly contagious diseases should be studied first and brought soonest under control, leaving for us of the present day the study and control of the less dramatic, more insidious and gradual, but no less fatal maladies such as heart disease and cancer. International coöperation and world-wide study have become the matter of fact procedure in dealing with the serious infections. The pioneer work of the Rockefeller Foundation and other groups transcending national boundaries have broken the ground and shown the way. It should not then be too hard to follow their footsteps in the collection of invalu-

able information about the most important causes of heart disease and the incidence and severity of their effects on the heart under all sorts of conditions and in every corner of the globe. Nature has for centuries been conducting gigantic experiments as to the effect of climate, of type of work, of diet, and of local or world-wide diseases on men, women, and children of different races, that are spread out before our very eyes for us to record and to analyze, quite readily yielding information that might never be obtainable by our own experiments on man, although certain tests could be added to enrich the findings. Under the most exacting conditions animal experiments of this sort cannot be completely applied to man; important clues and discoveries can result from experiments on laboratory animals, but if we rely only on them we are letting go to waste an equally important source of information about heart disease.

Statistics from surveys are slowly accumulating in this country and in certain other countries but by different uncorrelated groups, making them often difficult or even impossible for direct comparison. We need a large, well organized study that can in a several year program collect information, not just from hospital clinics or private practice, but from entire communities that will really show how common are hypertension and rheumatic valvular disease and syphilitic aortitis and coronary disease in relation to climate and mode of life. Several well and similarly trained groups armed with good clinical observers, stethoscopes, sphygmomanometers, electrocardiographs, x-ray apparatus, and autopsy technique could in a few years accomplish more than the next century of desultory work, and cost less than a single air raid over a city at war.

Let me take up in more detail what we do know or think we know about the world incidence of the seven important types of heart disease today, first prefacing these observations by a few sentences about the normal heart and the less important kinds of heart disease.

What is the range of the normal heart? This to my mind is the hardest question of all and the one most in need of study. No two hearts are exactly alike; even identical twins have different electrocardiograms. We have a fairly clear idea of the average normal figures for pulse rate, blood pressure, heart size, and electrocardiograms at different ages and sizes, but the upper limits of normal and the width of the borderline between normal and abnormal are still in need of clearer demarcation. We are trying, for example, to determine by x-ray some better standard

than height and weight and body surface for the normal heart size; certain measurements of body-build undoubtedly are important and we are asking for the help of the anthropometrists in this study. And the normal electrocardiogram has not yet been completely described. Within the past two years we have discovered to be normal, inverted T waves in Lead 2 due to the effect of vertical position and rotation that once were labelled coronary T waves, and we have found that P-R intervals in Lead 2 of 0.20 or 0.21 second may be normal and not the result of heart block, due to an isoelectric beginning of QRS_2. These are simply examples of some of the things we are learning almost every day about normal variations. In the world-wide studies will we find that heart size and electrocardiograms and blood pressure vary with race and climate or are they dependent more on body build and mode of life?

The seven important types of heart disease that I shall discuss particularly are in the order of their importance first, the more common group, *hypertensive*, *coronary*, *rheumatic*, and *luetic*, and second, the less common group, *congenital*, *the cor pulmonale*, and *subacute bacterial endocarditis*. Of the *lesser causes of heart disease* many variations in incidence and degree occur in different countries and indeed in different parts of the same country. *Anemia*, for example, is rife where malaria and such diseases abound and there the anemic heart is fairly common with a variable amount of dilatation and murmurs which simulate valvular disease and in fact have even given rise to an exaggerated estimate of mitral stenosis, and hence of rheumatic heart disease in certain tropical countries. Porter of Richmond has recently made some helpful observations of the anemic heart in Puerto Rico. *Malnutrition* and *avitaminosis* are now widely recognized as possible causes of edema and even of cardiac abnormalities themselves, but in this part of the world such results are uncommon and in the far East, too, they are much less common than they were years ago. In parts of the world where medical advances have been greatest *thyrotoxicosis* no longer plays the role of exhausting occasional hearts that it did a generation ago before there were adequate early diagnosis and effective surgical treatment of thyroid disease. *Myxedema* was always a rare cause of heart disease and today the "myxedema heart" is almost non-existent. Other endocrine cardiac disorders are also rare so far as we now know. *Neoplasm of the heart*, either primary or secondary, is so rare the world over, so difficult

of diagnosis, and so non-amenable to treatment that it may be passed by with this mere mention. *Trauma* of the heart is rare except as the result of attempts at homicide or suicide and in the theaters of war; damage to the heart from accidents, like the so-called steering wheel contusion, is undoubtedly very uncommon but is liable to exaggeration in these days of traumatic neuroses. Practice in suturing wounds of the heart is rare with us in Boston but not so uncommon in certain Southern communities where icepicks and razors are handy weapons with which to settle arguments among the colored folk; and war surgery of the heart will probably receive an extra polish in World War No. 2. Finally, there are scattered through the world certain foci of *infection of unusual nature* so far as the rest of the world is concerned or of an unusual degree of some widely distributed infection. Thus, in Brazil cardiac trypanosomiasis or Chagas' disease has long been recognized as a common infestation of which we apparently see no examples in this part of the world; malarial countries report heart damage in severe cases not to be attributed to the anemia alone; remote regions are sometimes affected by diphtheria or trichiniasis where control is inadequate and the heart may be seriously involved. Further studies of such rare or localized types of heart disease are of more than academic interest to us, but they are not in any way comparable to the importance of the common and widely distributed types of heart disease.

Hypertension with heart disease following on its course has been reported now in every part of the globe, even in China, Arabia, and equatorial Africa where it had been thought to be very rare or even non-existent. No adequate statistics have as yet been collected but we do know that hypertension is much rarer in the tropics than in temperate climes and that it seems to have increased in Japan and China since, though perhaps not because of, the introduction of occidental modes of life.

In our own country with widely different climates and races and kinds of work, hypertension is common in apparently every part. Its relative incidence, however, varies, depending largely on the incidence of the other three common types of heart disease. In the Northeastern and Central States where rheumatic and coronary heart diseases are very common, hypertensive heart disease makes up only 20 to 30 per cent of the cardiac cases, but in the South, where rheumatic and coronary types are less common, the hypertensive type makes up 40 to 60 per

cent of the total. Would more extensive studies show that hypertension is fairly common throughout the civilized world, or does the American mode of life play a role? Do the hurry and bustle, the lack of leisure or the failure properly to utilize the leisure we have, and overnutrition play a part? Perhaps not, but I have the impression that hypertension as a disease most common among the most overnourished people cannot be matched by any disease quite so important that is common among poorly nourished people. Perhaps the nomad Arab, even with his malaria and syphilis, can teach us something about health. Lawrence has written of the Arabs' hard physical life and his diet of a handful of dates day after day with a gorging feast on roast mutton every week or two or three. The fast days as well as the feast days may do him good—at least he rarely has hypertension or apparent coronary disease or gall stones or appendicitis or peptic ulcer; so says a keen and reliable observer, the so-called "desert doctor," Paul Harrison of Muscat on the Persian Gulf.

Or perhaps diet and mode of life do not directly influence blood pressure in a serious way; there may be, as revived by Goldblatt, a greater renal factor in one country than another. If so, why? And perhaps such a factor may likewise be in some way connected with diet and mode of life. And where does heredity come in? Perhaps indirectly in the way we live. We certainly need much more light on these problems, and we have not adequately studied even our own communities for comparative statistics on the incidence of hypertension.

Given hypertension, is it better borne by the heart in some peoples than in others? Is the malignant type a characteristic of any particular group of persons?

The second important cause of heart disease, *sclerosis and obstruction of the coronary arteries*, is likewise a subject demanding much more extensive as well as intensive analysis. Available statistics, which are very inadequate, indicate that coronary heart disease is much more common in the white race and in the United States than elsewhere; for example, in our own Southern states more than twice as much was found in the Whites as in the Negroes, and in 1934 vital statistics gave a mortality figure six times greater for the United States than for Japan. In France, however, so Gallavardin told me some years ago, coronary disease is fairly common; he was the first man ever to collect personally as many as a thousand cases of angina pectoris for analysis, and that was in the pleasant valley of the Rhone. Approximately a third of the

cardiacs in our Northern States are listed as coronary in type, while in the South, even among the Whites, the percentage is apparently appreciably less; but satisfactory statistics are lacking.

A few years ago we found that 100 unselected cases of coronary disease under the age of forty showed a very high preponderance of males (96 to 4), and a large majority of overweight, underexercised city dwellers who used tobacco to excess. Which of these attributes are important? Certainly the sex, and yet well known as that is, it has passed with little notice. There must be something in the endocrine setup in the male sex that makes the male much more a target for early coronary disease than his female counterpart in business or professional life. Even if later studies prove this to be true, we may not be able to attack the sex factor itself, but we may be able to alter some of the other factors such as overnutrition and lack of exercise and excessive nervous strain. Is it true that farmers and heavy laborers have much less coronary disease than doctors and lawyers and politicians and business men? In my recollection I can remember having seen only two farmers with coronary thrombosis; the one in Vermont, however, had been a banker for twenty years before he became a farmer, while the one in Maine had quit active farming ten years earlier to travel the countryside in his car as a political appointee. Such data are very unreliable and farmers are notably uncomplaining about their casual ills; a real survey of farming communities with careful questioning and electrocardiography is needed for comparison with a similar city survey to settle the problem which is obviously a most important one. The matter of family and racial inheritance is here intriguing—at one end of the scale is the high incidence among Jews and at the other end, the low incidence among Negroes. Can a person with a high and early incidence of coronary disease among his forbears break the spell by following a special mode of life, or is he doomed? It is my impression that he is, at least to a certain extent, the master of his own fate. Should he move to any particular climate, if he can, or type of community? Should he eat certain foods, low perhaps in cholesterol fats, as advised by Leary and Joslin? How much exercise should he take? And how much rest? How often vacations? How much mental work? Some of these answers we can doubtless get from a world-wide survey such as I have envisaged above.

On the other hand, in this matter of coronary disease and of hyper-

tension, too, there are other things to think of besides heart health alone. There is doubtless possible a compromise between the extremes of valetudinarianism and casual neglect, but there are two quotations in this connection that I would like to read you; they revert somewhat to my comments on Solomon's proverb. The first is from Plato in the Dialogues as cited by Osler: "'Before the time of Herodicus, the guild of Asklepios did not practice our present system of medicine, which may be said to educate diseases. But Herodicus, being a trainer, and himself of a sickly constitution, by a combination of training and doctoring found out a way of torturing first and chiefly himself, and secondly the rest of the world.

"'How was that?' he said.

"'By the invention of lingering death; for he had a mortal disease which he perpetually tended, and as recovery was out of the question, he passed his entire life as a valetudinarian; he could do nothing but attend upon himself, and he was in constant torment whenever he departed in anything from his usual regimen, and so dying hard, by the help of science he struggled on to old age.

"He goes on to say that Asclepius did not instruct his descendants in valetudinarian arts because he knew that in well-ordered states individuals with occupations had no time to be ill. If a carpenter falls sick, he asks the doctor for a 'rough and ready cure—an emetic, or a purge, or a cautery, or the knife—these are his remedies.' Should anyone prescribe for him a course of dietetics and tell him to swathe and swaddle his head, and all that sort of thing, he says, 'he sees no good in a life spent in nursing his disease to the neglect of his customary employment; and therefore bidding good-bye to this sort of physician, he resumes his ordinary habits, and either gets well and lives and does his business, or, if his constitution fails, he dies and has no more trouble.'"

The second quotation is from Edna St. Vincent Millay:

"My candle burns at both ends;
It will not last the night;
But ah, my foes, and oh, my friends—
It gives a lovely light!"

And yet one need not insist on dying with one's boots on.

Our third main problem is *rheumatic heart disease.* Here too the fundamental cause is unknown, and the incidence of the disease through the world very inadequately explored, but there are some things about

it that are clear to us today. In the first place, it is most common among the poor people where the living conditions are worst in any given community—there is no doubt about that. Secondly, there is a fairly high familial incidence. Thirdly, it is much more common, at least in severe form, in the temperate than in tropical climates, and its incidence increases steadily, other things being equal, from south to north in the temperate zone of the Northern Hemisphere and from north to south in the Southern Hemisphere. Fourthly, Streptococcus hemolyticus throat infections are particularly prone to set off an acute rheumatic infection. Fifthly, this rheumatic infection leaves a damaged heart in 75 per cent of the children who have it in New England, very preponderantly the highest incidence of heart disease resulting from any infection in this part of the world. And finally, the acute rheumatic infection or reinfection is more often responsible than any other factor for cardiac dilatation and myocardial failure in rheumatic heart disease, apparently at any age. From the standpoint of world-wide studies, here are three important facts already established but not adequately studied, namely, the effect of living conditions, the effect of climate, and the effect of streptococcus infection as the chief exciting factor. It may well be that the last two mentioned facts are directly related, namely, that the lower incidence of Streptococcus hemolyticus infections in the tropics is responsible for the lower incidence of serious rheumatic heart disease there.

Despite this knowledge there are occasional surprising discoveries. For example, I was amazed to come across numerous cases of acute rheumatic heart disease in the Cardiac Clinic of the General Hospital in Mexico City two years ago this month in most beautiful climate and ideal mild weather. I thought the altitude of 8,000 feet might have something to do with this but the doctors told me that some of the cases came from the lowlands at sea level along the coast in really tropical country. One might perhaps blame poor living conditions, for these patients were almost wholly native Indians who lived for the most part in rather primitive ways. But a fuller analysis of those findings is in order. Incidentally I also discovered that Streptococcus hemolyticus throat epidemics were by no means rare in Mexico City and the surrounding countryside—one was in progress while I was there. To various medical friends of mine in the United States these observations were as complete a surprise as to me, showing how ignorant we are of

what goes on not only in our own hemisphere, but even on our own continent and at our very door.

In New England, and in the Rocky Mountains, at least a third of all the cardiac patients are rheumatic in type. New York, Illinois, Iowa, and Minnesota have about the same or slightly less; Virginia, West Virginia, the Pacific Northwest and California have distinctly less, between 20 and 25 per cent; Texas, Tennessee,* and Oregon have been reported as having 10 to 15 per cent; and the Negroes in the Southern States as having 5 per cent or less. One of the most interesting observations of all has been that of Paul and Dixon who reported in 1937 that rheumatic heart disease was almost ten times as frequent among western Indians living in the cold, relatively dry regions of Wyoming and Montana close to the Canadian border, as it is among similar groups living close to the Mexican border (in the warm dry climate of southern Arizona). Thus climatic conditions seem to supersede race in susceptibility to rheumatic heart disease. Nearly 1 per cent of the school children of Boston, New York, and Philadelphia a few years ago had rheumatic heart disease while only one-sixth of that number were so affected in San Francisco and one-third in Cincinnati.

Apparently England has as much rheumatic heart disease as we have hereabouts and as many as 26,000 new cases of rheumatic fever annually have been reported for Scotland. On the continent of Europe, however, it is said to be not so common, with perhaps the incidence found in Virginia, and much rarer as one travels eastward (Pines tells me that the ratio of rheumatic heart disease to hypertension in Poland is about 1 to 50). In Arabia Harrison has encountered only a few cases of rheumatic heart disease each year. In India it is not rare, but some cases of anemia there had at first been wrongly called mitral stenosis. In China there have been conflicting reports but it seems likely that there are more cases in the North than in the South. In Australia a low incidence of rheumatic heart disease is reported and in the West Indies and in Venezuela it is said to be very rare. An accurate world-wide survey of the incidence of the rheumatic infection and of rheumatic heart disease is in order, for here, even more than in the case of hypertension and coronary disease, the practice of preventive medicine appears possible in the future.

* A recent paper (Swanson, H. Combined Syphilitic Aortitis and Rheumatic Disease of the Heart, *Am. Heart J.*, 1939, *18*, 672) reports the finding of about as much rheumatic heart disease as syphilitic aortitis at Nashville.

The last of the common types of heart disease, *cardiovascular syphilis*, in reality luetic aortitis, is no longer common with us in New England. Under our very observation it has apparently halved in its incidence in the last 25 years, from about 4 per cent of cardiac patients in the community at large to about 2 per cent, and in private practice to less than 1 per cent. Autopsy figures give a higher incidence, but at least half of the cases showing aortitis at autopsy have only a slight non-clinical degree, active or inactive. I have found in my efforts to establish a good teaching collection of pathological specimens from autopsies in my private practice that among the hardest to obtain because of their rarity are illustrations of luetic aortitis.

It is, of course, well-known that in some parts of this country and elsewhere in the world cardiovascular syphilis is common, several times, at least, more common than in my own experience noted above, and comprising as many as 32 per cent of one series of Negro cardiacs in Texas, but even so there are some interesting facts that are not so well known, and a number of questions to be answered. Among the Negroes in the South aortic syphilis is quite common but not so common as is hypertensive heart disease, which rated as high as 51 per cent of the Texas Negro cardiacs referred to above. Also, the high incidence of aneurysms and of comparatively early deaths of the Negroes with aortic syphilis may be ascribed not alone to their neglect of specific therapy but to the nature of their work; heavy labor is their common lot and that is not the best treatment for a weak aorta or a stretched aortic ring. In this connection some comparative statistics of the health of soldiers is of interest. In 1870 Myers, Surgeon to the Cold Stream Guards of the British Army, published a prize essay on the soldier's heart and stated that one British soldier per thousand in the service died of aortic aneurysm in the 1860s—he incidentally blamed chiefly the tight collar of the army uniform for this high incidence. Contrast this with the report of the Surgeon General of the United States Army for 1938, seventy years later, in which it is recorded that only one man out of 175,000 officers and men died as the result of an aortic aneurysm. Myers might have said, had he known what would happen, "You see what the change to a comfortable uniform has done." Another interesting fact is that in some parts of the world syphilis is apparently so attenuated in its effects that serious aortic involvement is rare. In Arabia, for example, where syphilis is almost universal, Harrison states that he had

encountered only three aortic aneurysms in 25 years. Thus there seem to be two diametrically opposed groups where luetic aortitis of clinical importance is low in incidence: one, the community where syphilis in the first place is not a very common disease and when it does occur is quickly diagnosed and adequately treated, and the other, the place where syphilis has been present in almost every one for generations and little or no treatment has been taken. There are other interesting relationships that need further enlightenment but it is obvious now that cardiovascular syphilis is not only a preventable disease but that we are living in the course of its actual prevention.

The first of the lesser causes of heart disease is that of the *congenital anomalies*, making up 2 per cent or more of all our cardiac cases and 10 to 15 per cent of cardiac school children* in New England and about half of the cardiac children in San Francisco. Since, however, the incidence of rheumatic heart disease is much lower on the West Coast than in New England, it seems probable that congenital heart disease occurs with about the same frequency in both places. Thus, the congenital heart figure of 1/7th of the 1 per cent incidence of the total heart disease found in the school children of Boston is to be compared with the 1/2 of the 1/3 per cent incidence in San Francisco. It is possible that the incidence is the same the world over, but of that we have no assurance whatsoever. It would indeed be of interest to know. One of the chief reasons why statistics of congenital heart disease have been slowest to accumulate is the difficulty of diagnosis that held sway everywhere until recent years and still rules today in most parts of the world. However, in the most enlightened communities great progress in diagnosis has been made in the last generation, greater in fact than in the case of any other type of heart disease (except so far as the occlusion group of the coronary type is concerned). After the first year of life not only has the diagnosis of congenital heart disease become relatively easy, but even the differentiation of the various anomalies has become possible in the majority of cases. It is in the first year that the greatest difficulty remains and it is in that same year that a large percentage of these children die, estimated at about 50 per cent at the Children's Hospital in Boston; such are the cases naturally with the gravest anomalies.

It once was said that it is idle to bother with congenital heart disease

* If young infants are included in estimating the incidence of congenital heart disease among the cardiac children in New England the ratio of congenital to rheumatic heart disease is about 1 to 4, instead of 1 to 10 or more, as noted in the older children.

because of the impossibility to prevent it, the difficulty to diagnose it, and the absence of any treatment for it. Not only are these prophets being shown to be in error as to diagnosis, but treatment, too, is developing, as witness the growing number of cases of successful ligation of the patent ductus arteriosus and the increased longevity of even very serious cases by methods of special care. It is also conceivable that in the future there may even be a reduction of intrauterine infection or other diseases, or of defects of germ plasm responsible for congenital anomalies of the heart.

The second of the lesser causes of heart disease is the most serious of all—*bacterial endocarditis*. Included here are both acute and subacute infections and all sorts of bacteria but only one of the lot ranks as important, namely the *subacute Streptococcus viridans endocarditis*, because the acute cases are almost always superimposed on fatal infections elsewhere in the body, such as pneumococcus pneumonia or staphylococcus septicemia, and are rarely diagnosable terminal processes, while subacute infections by other than the Streptococcus viridans are very rare. However, at the outset it should be recognized that the Streptococcus viridans itself is not just one simple strain; it is made up apparently of a whole variety of strains which not only react differently to different individual hosts but also react differently to different chemical agents. This fact is especially important now because of the recent introduction of a whole series of new chemotherapeutic agents which range all the way from the original sulfanilamide through sulfapyridine, sulfathiazole, and sulfamethylthiazole to the newest preparation of all, sodium paranitrobenzoate, just reported at meetings in New Orleans as being more or less specific for this very organism, Streptococcus viridans.

Subacute bacterial endocarditis is almost invariably engrafted on congenital or rheumatic heart disease, causing death in some 10 per cent of the former and 5 per cent of the latter. Its incidence in New England is about 2 per cent of all cardiac cases and in most other parts of the world, where the rheumatic heart is less common, subacute bacterial endocarditis is also rarer; but we possess very inadequate data about its frequency the world over.

The great dread of this type of heart disease is due to its almost invariably fatal ending after a long drawn out miserable illness lasting on the average six months. For many years, in fact ever since the disease was first recognized, innumerable physicians have watched thousands of

patients slowly die, unable to do anything to save them; about one in a hundred recovered, more or less spontaneously. In the last year or two the picture has begun to change and a few patients are still alive and in fact seem quite well, months longer than it appears likely they would have been in the old days, as the result of the administration of the new chemotherapy already mentioned, with the possible additional aid in some cases of the effect of heparin in reducing the number or size of endocardial thrombi. It seems possible that we are at the dawn of a new day in the treatment of this dread disease; it is not alone a reduction of mortality that is being effected but a control of the severity of the disease in many of the uncured cases. The next few years will witness a crucial struggle against this infection which should be waged the world over.

Finally, we come to a very difficult but intriguing problem, the incidence of the *cor pulmonale*, or heart disease secondary to disease of the lungs or of their blood vessels (pulmonary heart disease). Even in the most advanced medical centers we have no exact information as yet. The reason is that high disabling degrees of the condition are apparently rare and one must make unusually careful measurements of the muscle bulk of the right ventricle (in the absence of failure of the left ventricle) to pick up the lesser grades. Undoubtedly in these lesser but unimportant grades the chronic cor pulmonale is not so rare as it was once thought; Scott has found this to be true recently in Cleveland. On the other hand there has been a good deal of confusion caused in the past by mistaking the symptoms and signs of the underlying pulmonary disease itself for evidence of heart failure secondary to such lung disease, with lack of realization of the simple fact that when the right heart fails, the chief evidences of such failure are to be found in elevation of the systemic venous pressure with engorgement of neck veins and liver, and not in congestion of the lungs. As the result of these various difficulties we know next to nothing about the true incidence of the cor pulmonale the world over or even of the amount of its severer grades. We do know that in certain mining communities and perhaps in certain countries where extensive pulmonary disease is frequent, the cor pulmonale is much more common than in other parts. With us in New England apparently no more than one in fifty cardiac cases has the cor pulmonale; in some parts of the world, where rheumatic and syphilitic heart diseases are not frequent and silicosis is common, the proportion

of cases of the cor pulmonale might easily be many times greater. The field for this study is wide open and it is obvious that preventive medicine, so far as the cor pulmonale is concerned, has a promising future. Fortunately the so-called primary pulmonary endarteritis obliterans as a cause of right ventricular strain is a rare curiosity—I can recall having seen, to recognize, only three cases in the last twenty years.

Before leaving this discussion of the types of heart disease it should be noted first, that many cases show combinations of several factors, particularly of hypertension and coronary disease, and of rheumatic scarring and Streptococcus viridans infection, and second, that it is occasionally impossible to fit every case into any one or two pigeonholes—we must leave open a space for unknown etiology which may even allow our curiosity to establish new types in the future or to clarify causes that are at present obscure. Is it possible, for example, that repeated or prolonged paroxysms of excessive tachycardia may result in slight or progressive enlargement of the heart even leading to eventual failure without the intervention of well-recognized factors of heart disease? We know that in infants extreme tachycardia may cause cardiac dilatation and failure, which may even be confused with what used to be called congenital idiopathic hypertrophy of the heart. The effects of high altitude and of prolonged excessive physical effort on the heart of man have also been inadequately studied as yet and the question too of individual or even racial differences of myocardial resistance to strain, which brings to the front again the old story of the athletic heart.

Having presented the specific problems of heart disease, I shall now put them together as the total problem, a far less significant survey, since we are then simply lumping together different diseases as they happen to affect one organ. Nevertheless, for the sake of completeness we should briefly survey the problem as a whole. Heart disease in toto easily heads the list of causes of mortality in the United States, with cancer second, while the former leaders of thirty years ago, tuberculosis, infantile dysentery, and pneumonia, have dropped to a good deal less than half their former rates; this drop in the infectious diseases undoubtedly accounts for the remarkable drop in death rate in Massachusetts from 60 per thousand in 1910 to less than 20 per thousand in 1934. And yet if we take any single one of the different types of heart disease, which are really distinct non-related conditions, it falls well

down the list, imposing though the whole collection may be.

An interpolation should, however, be made at this point concerning hypertension. This is really a disease in a class by itself because of its far reaching effect on various parts of the circulation; if it does not kill by heart failure it is likely to do so by apoplexy or by renal involvement. If we take from the 1932 United States Mortality Statistics the figures for cerebral hemorrhage, 95,000 deaths and two-thirds of the cases of chronic myocarditis, 60,000, and about half of the chronic nephritis, or 46,000, we undoubtedly have not far from a fair approximation of the cardiovascular effects of hypertension, something over 200,000 deaths, much more imposing than any other grouping except the total figure for diseases of the circulatory system, 295,000 (which does not include cerebral hemorrhage or chronic nephritis). It far transcends the so-called entity of arteriosclerosis. Cancer was only 129,000 and tuberculosis but 75,000. This is another illustration of the value of separating the causes of heart disease for consideration on their own, as we have already done in this paper, but which is very inadequately done in the routine mortality statistics—a reform here is in order and the vague terms acute and chronic myocarditis should be replaced by more accurate designations, such as hypertensive heart disease, or myocardial infarction, or cardiac enlargement of unknown cause. It has been my experience that the great majority of cases of so-called myocarditis can be subdivided into 1) big hearts due to hypertension, 2) coronary heart disease, and 3) neurocirculatory asthenia.

In 1932 the total death rate for the whole United States was 10½ per thousand. Twenty-three per cent of these deaths were recorded as due to disease of the circulatory system, too low a figure undoubtedly since cerebral hemorrhage and chronic nephritis are not included. It is of especial interest to note that there was a considerable variation in this percentage between the Southern and Northern States, with but relatively little variation in their death rates; the Southern States gave figures consistently under 20 per cent, dropping as low as 12 per cent in Mississippi (this figure, by the way, held also for Hawaii), while the Northern States were consistently over 20 per cent, rising as high as 30 per cent in Massachusetts.

A quarter of a million persons in the United States were recorded as having died from heart disease in 1930, more than half of whom (140,000) succumbed before they were 70 years old. That's where

the rub comes. It should not worry us much, in fact we would rather be content, if all the deaths in the United States were from heart disease after the age of 75 with little or no earlier crippling from the condition. This would be a good way out for us. But it will, I fear, be a long time before we reach that goal. The prolongation of the average life in this country in the last hundred years has been amazing, doubling itself in that length of time to an age now well over sixty. That next decade, however, is bound to prove the greatest hurdle, and we can't jump it until we have done more than we have to date with the control of hypertension, coronary disease, rheumatic carditis, and syphilitic aortitis. The factor of syphilis is definitely on the decline, the rheumatic infection seems also to be less serious; although we have some idea of what to do to check these things, we must not relax our efforts one iota. It is, however, against hypertension and coronary artery sclerosis, especially as they affect youth and middle age, that we must now direct our newest attacks. It is in our own country that these diseases seem most rampant and yet one often hears the boast of our prowess in preventive medicine. Do not let us delude ourselves into thinking that we are so healthy while we harbor these insidious but serious evils right in the very centers of our most advanced civilization, in fact in the very hearts of our own medical profession and public health organizations. The challenge is before us: "Physician, heal thyself." It seems to me that while we have been doing fine work in the control of infections and industrial diseases of all sorts in the past generation or two, we have neglected the most simple rules of health laid down through the ages, which balance exercise with rest, overeating with fasting, and excitement with relaxation, not a humdrum life at all but a most rational one for body, mind, and soul. The ancients got fat and nervously exhausted doubtless, but food was not so plentiful for everyone as it is now, chariots were relatively few, and not many of them travelled as fast as the slowest antique motor car at its slowest speed today. I can't escape the conviction that if our present generation used its intelligence and its legs more, and its alarm clocks and its stomachs less, we might have fewer cases of the coronary disease and of the hypertension that so beset us. However, until we have more accurate world-wide information about these things than we possess today, this conviction of mine must continue to be rated simply as an impression, attractive as it may be, on the basis of our clinical observations and of deductions as to the

Creator's plans of the function of muscles, nerves, and circulation.

Let me close with a quotation from Hermann Biggs himself. In 1904 in an address on *Preventive Medicine* before the fifty-fifth annual session of the American Medical Association at Atlantic City he said, "The terms sanitary science, public or state medicine, and preventive medicine have frequently been used as almost synonymous. The latter term, 'preventive medicine,' however, has sometimes been restricted in its application to the prevention of the infectious diseases. In the broad sense, preventive medicine comprises both general prophylaxis and individual prophylaxis, and applies to all forms of disease, not simply to the infectious diseases. Preventive medicine is an applied science, which deals with the preservation of the health, both of the individual and of the community.

"No subject more vitally concerns the welfare of a community than that pertaining to its healthfulness. How the inhabitants live, and how and at what age they die, what is the extent and character of the morbidity occurring among them and what are its causes, are questions of momentous importance. They are essential features in the problem, whose solution will teach men how they may live longer, healthier, and therefore happier lives."

The author then discusses at some length the prevention of the infectious diseases but ends the article with the following remarks:

"A very difficult problem arises in connection with the diseases of the circulatory apparatus and the kidneys. My investigations have shown that in New York City a large increase has taken place, due to these causes, during the last twenty years. The acute respiratory diseases, cancer, and diseases of the circulatory apparatus and the kidneys are the only important causes of death which have shown an increase during this period. The increase in cancer amounts to about 15 per cent, and the increase in acute respiratory diseases amounts to about 15 per cent, while the increase in the diseases of the circulatory apparatus and kidneys combined equals about 40 per cent. In making this statement I have taken fully into consideration the possible influence of greater accuracy in the death returns, i.e., the inclusion formerly of these under other causes of death; but after making all allowances, it seems to me without question that an increase equaling 40 per cent has taken place." [Quite possibly some of this increase lamented by Biggs was due to his already effective prevention of some of the infections of early life

which was allowing relatively more persons to reach heart disease ages, as Drs. Bolduan and Cohn have pointed out.]

Biggs proceeds: "A very important sanitary problem is here presented to the health authorities. *What are the factors in the lives of the inhabitants of our large cities (for I have found that similar increases, less extensive, however, have taken place in London, Paris, and Berlin) which have caused such a remarkable increase in the prevalence of these affections, and how are these factors to be removed?*" [Italics mine.]

Thus Biggs already clearly recognized this problem of heart disease as one of preventive medicine, with world-wide significance 36 years ago. Can we answer his question? No, I believe not, except in minor details, but we have I hope a much clearer conception of the problems left to solve than was possible a generation ago. Vital leadership in finding the path has come from your own pioneer New York Association for the Prevention and Relief of Heart Disease and from the individual labors of Haven Emerson and many others who right here in New York accepted the challenge that Biggs laid down in 1904. I feel confident that much faster progress can be made during the generation that is to come than was possible in the generation that is past. *Tempora mutantur nos et mutamur in illis.*

THE MENOPAUSE*

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THE *climacteric* may be defined as that transitional period in women during which cyclic ovarian activity, resulting in menstruation, undergoes cessation. The term *menopause*, strictly speaking, refers to the actual cessation of ovarian activity. The problems arising as a result of this transition extend beyond quiescence of ovarian activity into the *postmenopausal* state. The endocrinological aspects of the problems arising at this period encompass, therefore, all three phases. While generally a spontaneous phenomenon, the menopause may be induced or accelerated by measures which depress ovarian function, such as radiation, or by the removal of the uterus or ovaries, or both.

Although the loss of ovarian secretion is the most important single event and initiates the series of changes which occur at this period, the climacteric must be recognized as a symptom complex involving the readjustment of the whole organism to a new type of internal environment. A change in the balance of the secretion of the ductless glands plays an important part in the reconstruction of this internal environment. Little is known of the exact nature of these changes. That the physiology of the thyroid is at least temporarily altered is apparent from the fact that nodular hyperplasias appear in larger numbers; that this is the age period with the greatest incidence of thyroid atrophy with myxedema; and that the development of Graves' disease is often an accompaniment. A change in the physiology of the pituitary manifests itself in an increased secretion of gonadotropic hormone. The alterations in the other ductless glands accompanying or resulting from the diminution of ovarian activity still remain obscure.

Other biological changes also make their appearance. The climacteric ushers in the decrescent phase of the life cycle of the organism during which the various processes of aging are accelerated and degenerative

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phenomena become correspondingly prominent. These are seen, for example, in the sclerotic vascular changes, in the development of hypertension, and in the degenerative changes in the various viscera and external structures of the body and in the skeleton.

On the psychological level there occurs, likewise, a reorientation of the woman to a new status in relationship to her environment and to her family. Various psychological disturbances ranging from psychoneuroses to the psychoses, of which involutional melancholia is an important example, make their appearance.

The complexity of the menopausal state is apparent and it has only been possible, since the estrogenic hormones have been available, to begin to differentiate between the phenomena due to ovarian insufficiency and those which are part of an even more fundamental rhythm in the life cycle of the species. The chief purpose of this paper is to examine those phases of the menopausal state for which ovarian insufficiency is largely responsible.

The cessation of menstruation at the menopause appears to be a consequence of the gradual aging of the ovary. The Graafian follicles gradually degenerate and disappear, the blood vessels undergo medial thickening with narrowing of the lumen, and fibrosis of the capsule with contraction, occurs. Watson, Smith, and Kurzrok[1] have shown the increasing insensitivity of the human ovary to gonadotropic stimulation with advancing age. The hormonal effect of these degenerative changes is a significant decrease in the production of estrogenic hormone. Concomitant with this is the appearance of gonadotropin of pituitary origin in the urine in far greater amounts than is ever seen during the normal menstrual cycle, during which it can only be detected for brief periods in the course of each cycle. An adjustment must be made to this new hormonal environment of which only these two aspects are known and which must be considered a physiological one for the species. The majority of women manage this successfully; those who are unsuccessful suffer as a consequence a variety of symptoms detrimental to their well-being. No certain knowledge exists as to the physiological influences which promote and those which interfere with this readjustment. Certainly, with respect to the known hormonal changes, there is no detectable difference between the women who adjust successfully and those who fail and we know of no other satisfactory criteria which differentiate between them.

The suggestion has been made that the symptomatology of the menopausal syndrome is due to an excessive production of gonadotropin on the basis of the observation that estrogenic therapy with symptomatic relief is accompanied by a marked reduction in the excretion of urinary prolan. However, Heller and Heller[2] were able to dissociate the symptomatology of the menopause and the concentration of urinary prolan. Their findings are in accord with similar experiments in our laboratory.[3] We must look elsewhere, then, for the factors responsible for this maladjustment.

The treatment of the menopause has made rapid strides in the past few years due to the brilliant work of the chemists who have provided us with specific and powerful estrogenic agents. The problems relating to the climacteric are, however, not solely the province of the endocrinologist and psychiatrist; organic changes in the reproductive tract should not be neglected.

The climacteric may proceed uneventfully and be characterized by a gradual waning of menstrual flow and by cycles otherwise normal. Menstruation may also cease abruptly with no preceding irregularities. Frequently, however, the transition is a stormy period marked by menstrual irregularities, menorrhagias and metrorrhagias which may precede the menopause by many years and offer diagnostic and therapeutic problems. The woman is now entering the age of the greatest incidence of carcinoma, hence such irregularities and bleedings gain significance. One cannot stress too much the desirability for careful gynecological examinations under such circumstances and I feel that it is a necessary precaution to insist that no endocrine therapy be instituted until the gynecologist can assure one of the absence of pathological changes and has corrected any inflammatory lesions, particularly about the cervix, which are felt to predispose towards the development of neoplasms.

Symptomatology of the Menopause

Symptomatology of the menopause is as bizarre and extensive as any syndrome with which I am acquainted. There are certain classic and well-recognized complaints which are most common and a second group of signs and symptoms which occur less frequently but are apparently specifically related to this state. Among the most common symptoms are the vasomotor, with the characteristic hot flush followed by drenching sweats, and the dizziness, palpitation and exhaustion which follow

the attacks. There are also the disturbances of peripheral circulation which take the form of paresthesias and numbness. Insomnia is frequently complained of and asthenia may be profound enough to prevent the patient from carrying out her duties, both domestic and social. In addition, there are a variety of gastrointestinal symptoms largely of functional character. One of the most uncomfortable complaints is of headache. Arthralgias and degenerative changes in various joints contribute to the picture. Changes are noted in the texture of the skin and subcutaneous tissues. Occasionally such phenomena as urticaria and angioneurotic edema are seen. With time, senile atrophic changes occur in the genital tract with attendant discomfort. In many patients there is a definite tendency to gain weight and to become aware of fat deposits different from those seen in early life. On the behavior level, the woman tends to become depressed, emotionally unstable, irritable and given to weeping. She is inclined to withdraw more and more into herself, feel insecure and become hypochrondriacal, resentful and suspicious. Other psychoneurotic manifestations may make their appearance or be exaggerated. The sexual life may wane in intensity although occasionally this period is associated with increasing sexual interest. Frank psychoses may be initiated.

Although these symptoms, which could easily be supplemented by many others, generally make their appearance on the cessation of menstruation, they are frequently seen during the period of transition. At this time it is not uncommon for them to be more marked premenstrually when estrin production is at its lowest and to improve or disappear with the development of the ovarian follicle during the first half of the cycle when the production of estrin is increased.

Choice of Therapeutic Agents in the Treatment of the Menopause

The proper therapeusis of any disturbance of the ductless glands is dependent on the availability of specific secretions of the glands involved and on objective methods to guide their use. The first of these criteria is fulfilled with respect to the secretions of the ovary. At present there are available three estrogenic hormones of known chemical structure and potency. These are estrone, which is the ketohydroxy estrin; estradiol, the dihydroxy estrin; and estriol, the trihydroxy estrin. Differing widely in their estrogenic activity by weight, equivalent results can be

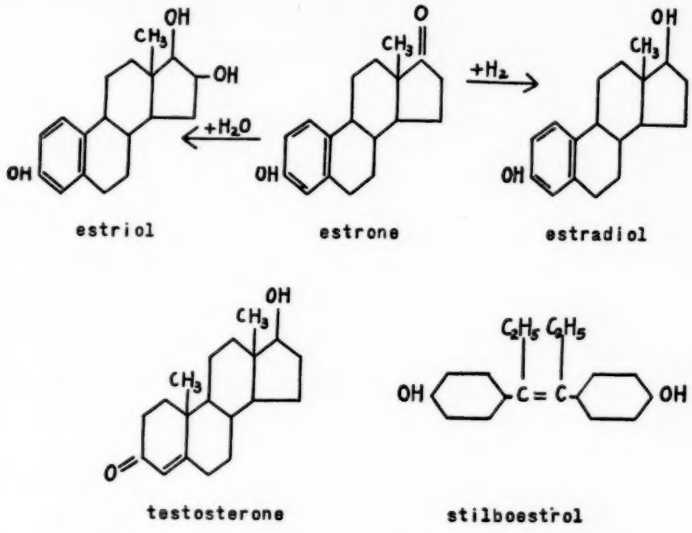

Fig. 1—Hormones used in treatment of the Menopausal Syndrome.

obtained with all, provided adequate amounts are administered. I have found estrone and estradiol to be the most effective and economical for replacement therapy in the human. Estriol preparations are designed for oral administration and should prove equally useful once they are made available at reasonable cost in sufficient potency. Estradiol is usually conjugated with either benzoic or propionic acid in an effort to prolong its activity. These estrogens are standardized in terms of rat and international units, the rat unit being derived from biological assay usually according to the method of Allen and Doisy. On the basis of their biological assay in the human, we have come to rely on the activity expressed in rat units, as the various estrogenic preparations we have analyzed have corresponded to each other in potency rather better on the basis of the rat unit than on the international unit. In addition to the natural estrogenic compounds, two synthetic estrogens have been employed, stilbestrol and ethinyl estradiol; and, interestingly enough, the androgenic hormone, testosterone, conjugated with propionic acid, has proved itself an agent capable of ameliorating menopausal symptoms.

The second criterion, objective methods for the applications of these therapeutic agents, has also been fulfilled to a large extent. Several

Fig. 2—A characteristic menopausal smear prior to treatment with estrogens. Note small oval "deep" cells, undifferentiated squamous cells with large nuclei, cell clumps, bacteria, smudgy appearance, and absence of cornified cells.

possible indices can be employed. It has been suggested that, since the estrogens reduce the initially high titer of urinary gonadotropin of the menopause, the disappearance of this hormone from the urine might serve as an index of full replacement therapy. The disadvantages inherent in the use of this method are that it is laborious and still far from exact. Furthermore, the appearance and disappearance of urinary prolan in relation to symptomatology[2] and vaginal smear changes[3] have been found to be inconstant and unreliable. The estimation of an elevation of the estrin level in the urine following replacement therapy is also a laborious and time-consuming procedure. Endometrial biopsies to detect

Fig. 3—Follicular vaginal smear after estrogenic therapy. Note that all cells are typically cornified, with small pyknotic nuclei, discretely arranged in a clear field free of debris. This represents the peak effect of replacement therapy with estrogenic hormones. When this smear picture is attained, all symptoms due to ovarian insufficiency per se should disappear. (Papanicolaou and Shorr, Reference 4.)

estrogenic effects are associated with trauma and are inconvenient to obtain with any frequency.

In 1935,[4] the vaginal smear was introduced as a method for evaluating the effect of estrogenic hormonal therapy in the human. During the menopause, as a result of the low estrin production, the vaginal epithelium undergoes considerable atrophy. The desquamated vaginal secretion, when aspirated by a simple glass pipette, placed on a slide and stained, reflects faithfully the state of the vaginal epithelium. During

the menopause, it presents a typical picture, quite different from that seen during the normal menstrual cycle. It is free of cornified cells, the squamous cells are of the intermediate type and there are varying numbers of small, round or oval cells from the deeper layers of the epithelium. Bacteria, leukocytes, cellular debris and occasionally red blood cells are to be seen. The smear presents a "smudgy" or "dirty" appearance. When estrogens are given in adequate amounts a series of changes takes place in the smear until it is transformed into one similar to that seen mid-menstrually in the normal cycle. This induced follicular phase is characterized by the presence of cornified cells which are usually discrete, by the absence of leukocytes and debris, and by a clear appearance. At this stage, which represents the peak effect of estrogenic therapy, all of the symptoms due to ovarian insufficiency per se should disappear whereas those of other origins will persist.

This method has the virtue of simplicity, specificity and the absence of trauma. In addition, it can be repeated as frequently as desired. By its use in man it has been possible to assay biologically the variety of estrogenic compounds available and to set up standards for their use. We had hoped by this method to arrive at a definite biological unit for man which would represent a full replacement dose just as the rat or mouse unit is equivalent to an estrogenic unit in these rodents. Had this been possible the therapy of the menopause would have been greatly simplified. We found, however, that individual patients varied greatly in the amount of hormone necessary to produce an equivalent biological effect. Though the "human" unit lay between 2,000-3,000 R.U. daily for most patients, a spread of as much as 1000 per cent, as from 1,000 to 10,000 R.U. daily, was observed. Therefore, as regards dosage, each patient becomes an individual problem.

It also became apparent that menopausal symptoms in different patients were not uniformly sensitive to estrogenic therapy. In about one-fourth of the patients symptomatic relief occurred with relatively little change in the vaginal smear; with about one-half, relief was experienced at intermediate levels; and with the remainder, complete relief was not obtained until full replacement and a follicular smear were achieved. With this, as well as all other objective indices employed, there is apparently no absolute correlation with symptomatology. The smear does, however, have particular value in dealing with the variety of bizarre menopausal symptoms, especially those of a psychoneurotic character,

since by insuring complete estrogenic replacement, it permits a differentiation between those complaints specifically due to ovarian insufficiency and those arising from other causes.

Given effective therapeutic agents and objective methods for guiding their use, we must now consider how best to apply them to the problems presented by the menopausal syndrome. There are two major therapeutic objectives, one is to abolish the complaints which result from failure to adjust to the new status; the other, to achieve as rapidly as possible a satisfactory adjustment which will free the patient from further need of such exogenous support. This program must deal with questions of dosage, the modes of administration as regards effectiveness, convenience and economy, the possible dangers of neocarcinogenesis, the influence of therapy on the eventual readjustment, and the problem raised by the effects of estrogen on the endometrium.

To some of these questions there are fairly satisfactory answers. To others, our present incomplete knowledge permits of no final conclusions.

Much can be said with certainty as to the choice of preparations and the modes of administration. Those estrogenic agents which have proved effective in man have been discussed above. The choice of the mode of administration is largely an economic problem. Estrogens are at present generally employed by the intramuscular route because this is the least expensive. They are also effective by mouth but as they lose so much of their activity by this route, from 10 to 20 times the parenteral dose must be given to obtain the same estrogenic effect. This loss of efficiency by mouth should be kept in mind when transferring from the parenteral route, and it would be desirable to have all estrogenic preparations designed for oral administration standardized in terms of actual activity corrected for this loss of potency. One such preparation is so labelled. The topical application of estrogens in pessary form for the discomfort associated with senile vaginal changes is the accepted method of dealing with this condition. In addition to these routes, Bishop[5] and Salmon, Walter and Geist[6] have introduced crystals of estrogenic hormone subcutaneously. This has proved economical and effective by virtue of the slow absorption of the crystals, and the action of the estrogen has been greatly prolonged. It will be of interest to see whether such prolonged action on the endometrium will result in bleedings which cannot be well controlled. This has apparently occurred in 4 of 20 patients treated with

implants by Twombley.[7] This problem does not exist in the absence of the uterus. The final choice will undoubtedly be the oral route once the cost of estrogens is lowered. One such estrogen, stilbestrol, which is very effective by mouth and is inexpensive, has been synthesized and has aroused great interest because of these properties.

Questions relating to dosage and the best methods for regulating therapy cannot as yet be answered with similar definiteness. Our relatively brief experience with estrogenic agents has not as yet permitted the recognition of the best principles on which to base a therapeutic regime. The wide variations from patient to patient in the subjective and biological response to estrogens make any attempt at standardization of dosage futile. There is likewise no general agreement as to the extent of symptomatic relief to be aimed at. An equal uncertainty exists as to which regime is best adapted to permit the hoped-for readjustment to the menopausal status.

The regime adopted in this Clinic may be briefly set forth with full appreciation of what may prove to be its shortcomings. It is based on the control of hormonal therapy by means of the vaginal smear rather than on subjective symptoms alone. Following a pelvic examination to rule out organic disease, and a psychological evaluation, the patient is placed on graded doses of an estrogen until a full follicular phase is reached. This represents complete replacement therapy. The first course of treatment extends over 4 to 5 weeks during which a correlation is made between the degree of smear change and the extent of subjective relief. This permits the observer to judge the sensitivity of the individual response to the estrogen, the level of dosage and the smear change at which optimal effects occur, and the character of the symptoms for which ovarian insufficiency is specifically responsible. One is frequently struck by the greater well-being which can be achieved in this way than when subjective indices such as the flush are relied upon exclusively. The results of this first course of therapy serve as a guide for further management.

Treatment is then interrupted. The speed and intensity with which symptoms recur enable one to form an opinion as to the severity of the syndrome and the probable ease or difficulty of the eventual readjustment. The second purpose of the rest period is to permit the regression of the induced endometrial hyperplasia in order to avoid the discomfort of bleeding from a too-prolonged uterine stimulation. Bleeding

will, however, occasionally occur and its significance should be made clear to the patient.

Treatment is resumed after a two-week interval if the return of symptoms warrants it. The dosage and level of the smear which afford optimal relief is now selected. Excessive dosage is thus avoided and the full benefit inherent in the therapy realized. The response of the patient to this regime is extremely variable. With favorable cases, each succeeding course finds optimal symptomatic relief achieved with progressively smaller doses until the need for further support ceases entirely. In the unfortunate, large doses may be required for many years with little or no evidence of an impending readjustment. All stages between these extremes are seen. Along with the hormonal therapy every effort is made to deal with other factors which may contribute to the persistence of symptoms. Of most value in this respect is the psychotherapeutic approach.

The problems involved in spacing the treatment deserve brief comment. Where oral administration is possible, it is most efficient to give the hormone daily. When the intramuscular route is employed the inconvenience of daily injections is usually an obstacle to the maintenance of an even concentration of hormone in the body. It can be shown by studies of the vaginal secretion that the more widely spaced the less efficient are injections of estrogens even if conjugated with benzoic or propionic acid. The practice of giving large doses of estrogen at long intervals is not only inefficient but carries with it whatever dangers may be inherent in the marked and repeated shifts in the histology of the endometrium change it induces. In the hysterectomized patient this difficulty does not exist but the possible effects on the breast must be borne in mind in relation to malignancy.

Concern has been expressed lest intensive estrogenic therapy delay the eventual readjustment. This has led many workers to recommend that the dose be just that which allows the patient to be comfortable and that it be steadily and systematically reduced with a view to assisting the readjustment of the post-menopausal status. This regime may prove satisfactory for some patients but for the most part I have been unsuccessful in accelerating readjustment by such an enforced reduction in dosage. It is my impression that estrogenic therapy per se does not interfere with the eventual transition and that there is little reason to withhold the full benefit inherent in these therapeutic agents.

This chapter would be incomplete without reference to the management of menopausal symptoms arising during the climacteric prior to cessation of menstruation.[8] These symptoms are occasionally as severe as those seen at the menopause. While they may occur throughout the cycle, they are more commonly present premenstrually and during the flow, disappearing with the increased estrin production of the developing ovarian follicle. They respond equally well to replacement therapy. When they occur premenstrually they are best treated by the administration of estrin from the mid-point of the cycle up to a few days before the expected flow. When they occur at menstruation the flow need be no contraindication to the administration of estrogen, in the absence of pelvic disease. Not infrequently it serves to reduce the excessive flow which may occur in the climacteric. The dose on the first and second day should be relatively small, for example, about 500 R.U., and may be raised on the succeeding days until the symptoms disappear. It is often helpful when symptoms occur during menstruation to administer the hormone for a short period premenstrually as well. When symptoms occur throughout the cycle, estrin should be administered throughout. As at the menopause, no standard dosage can be prescribed. The average patient experiences relief with 1,000-2,000 R.U. three times weekly except for a 3 to 4 day period prior to the expected flow, but here again each patient presents an individual problem.

The Synthetic Estrogen, Stilbestrol

This interesting therapeutic agent, diethyl-stilbestrol, was synthesized by Dodds and his associates in 1938.[9] As may be seen from its formula, it differs from the natural estrogens in that it does not contain the phenanthrene-ring system formerly thought to be necessary for estrogenic activity.

It was found to be an extremely powerful estrogenic agent in animals, suffering little diminution in potency by the oral as compared to the parenteral route. It reproduced virtually all the effects of the natural estrogens in animals and was about two and one-half times as active as estrone by injection. By mouth, its superiority over the natural estrogens was even more striking. It will be recalled that the natural estrogens, estrone and estradiol, like the thyroid hormones, are effective by mouth. However, about 15 to 20 times the parenteral dose must be administered orally to produce the same effect, as judged by vaginal

smears. Stilbestrol, on the other hand, lost half or less of its activity by mouth. These attributes, its high estrogenic activity, its oral efficiency, and its cheapness, gave promise of a wide usefulness in human therapy. Preliminary experiments on animals had indicated that it was devoid of toxic activity.

The first reports of its clinical use were highly favorable.[10,11] Stilbestrol reproduced all the effects observed with the natural estrogens, including the relief of menopausal symptoms. More extensive clinical studies, while confirming its estrogenic properties and attendant relief of symptoms, brought out certain undesirable side reactions chiefly referred to the gastrointestinal tract, and consisting of nausea, vomiting and anorexia. Also evidence began to accumulate from toxicity studies that its use in animals was sometimes followed by damage to various tissues, especially the liver.

Our own experience with stilbestrol[12] was derived from a study of a series of forty-four women, two of whom had primary amenorrhea, in whom estrogenic activity was the chief point of interest, and forty-two with the menopausal syndrome, who permitted an evaluation of its effects on symptoms. The estrogenic effects were followed by vaginal smears and biopsies. The therapeutic goal in each patient was the induction of a full follicular smear as well as symptomatic relief. The results of our study may be briefly summarized as follows.

We could confirm the previous observations that stilbestrol is a powerful estrogenic agent losing little of its potency by mouth and capable of ameliorating subjective symptoms of the menopause. The oral estrogenic unit for the human was found to lie between 2 mg. and 4 mg. daily.

Its use, however, was associated in our series with a high percentage of toxic symptoms in the form of nausea, vomiting, abdominal distress, anorexia, diarrhea, lassitude, paresthesias, vertigo, thirst, and skin rashes. There appeared to be no relation between the size of the dose and the development of toxic reactions; nor was there evidence of an acquired tolerance to the drug. The side effects appeared to be largely central in origin since they followed injection as well as oral administration. Liver function tests were inconclusive.

The incidence of side effects in the group of patients studied was a good deal higher than other workers have reported. Their existence, however, whatever the incidence, certainly warrants caution in the use

of this preparation and our feeling is that, until the nature and significance of the toxic effects are understood, it should be regarded as an experimental preparation.

One is tempted to speculate on the nature of the toxic results obtained with stilbestrol. It is of interest that the two synthetic estrogens, stilbestrol and ethinyl estradiol, have this in common, that they are both very potent by mouth and both produce the same type of toxic side reaction. The explanation for the loss of potency of the natural estrogens by mouth is held to be their degradation during passage through the liver. This organ has been shown to have the capacity to destroy natural estrogens by some still obscure process. The synthetic estrogens apparently escape this degradation in the liver. At least such an explanation would account for their oral potency. Such a mechanism may function to prevent the accumulation of estrogens in the circulation above levels which are adequate for their effects on the structures they specifically influence. An excessive accumulation in the blood stream might have an unfavorable effect on other structures in the body. We may well be witnessing with stilbestrol those undesirable effects which are prevented with the natural estrogens by this mechanism of neutralization. The greater oral potency of stilbestrol may therefore be gained at the expense of the safety of the organism.

The Male Sex Hormone in the Menopause

The history of the use of male hormones in disturbances of female sex physiology is an interesting one. The existence of both hormones side by side in both sexes still awaits a full explanation. Animal experiments in which the balance between estrogens and androgens has been altered artificially, have afforded some clues. The first effect observed was an inhibition of the pituitary with a subsequent suppression of the estrous cycle; the second was a neutralization of the peripheral effects of estrogens on the secondary sex structures. A similar type of action has also been found in man. Loeser[13] first demonstrated the atrophic effects of androgens on the endometrium in women and pointed out its use in dealing with excessive bleeding. Studies from this laboratory[14] showed that human menstruation could be suppressed at will with androgens, to return when treatment was stopped. We were also able to demonstrate a peripheral antagonism between the male and female sex hormones in the case of vaginal epithelium.[15] The ratio of

androgen to estrogen, necessary to produce this effect, was about 50 to 1. This is far greater than the excretion ratio of these hormones in women. Hence the estrogenic influence predominates. In man, therefore, the same types of effects were to be observed as in animals—an inhibitory effect on the pituitary with subsequent suppression of menstruation, and peripheral neutralization of estrogens by androgens.

What was quite unexpected was that androgens should be capable of abolishing the symptoms of the menopause, although one property was common to both types of hormones, i.e., the ability to depress the excretion of urinary gonadotropic hormones of pituitary origin.[16] That the androgens were indeed capable of ameliorating the symptoms of the menopause became apparent from the work of Salmon[16] and others as well as from our own studies.[15] The effective dose was rather high, in the neighborhood of 25 mg. daily. The use of androgens in the menopause had one advantage; it was unassociated with any withdrawal bleeding, since its effect on the endometrium is to induce atrophy rather than hyperplasia.

However, disadvantages soon became apparent in the form of increased hirsutism, enlargement of the clitoris, and a lowering of the voice, unpleasant sequelae which often take a long time to reverse themselves. When one considers the duration of replacement therapy in the menopause, it becomes apparent that this symptomatic effect of the androgenic hormone, while of interest to the student of sex physiology, does not justify its use as a substitute for the natural estrogens.

Estrogens and Carcinoma in Man

One of the deterrents to the widespread use of estrogens in man has been a consequence of animal experiments demonstrating the capacity of these hormones to produce carcinoma under certain conditions. It is not yet clear whether the carcinogenic effect of the estrogens is direct or dependent on the release of genetic predispositions on the part of these animals. Whatever the explanation, there has been considerable concern over the possible effects of the extensive use of these hormones on the incidence of carcinoma in the human.

Conditions under which carcinoma is produced in animals differ in certain important respects from those under which the estrogens are ordinarily used in human therapy. Carcinoma is most readily induced in strains of animals having a high incidence of spontaneous carcinoma.

The amount of estrogen administered has been very large in proportion to the weight of the animals. Furthermore, the hormones must be given over a large part of the life span of the animals.

In humans it is impossible to assay the innate tendencies towards carcinoma; the duration of therapy is relatively short and the dose of estrogens ordinarily employed is physiological, approximating the quantity elaborated in the normal economy of the organism.

This problem cannot be approached as directly in man as in animals, for one cannot deliberately seek to bring about the production of carcinoma in man except under unusual circumstances. We are, therefore, forced to evaluate the significance of estrogenic therapy in the human by analyzing the incidence of new growths in large series of cases in which the hormones were used for a sufficient length of time to make this evaluation significant. Other methods of approach take the form of studies of the histological changes in the uterus after prolonged therapy.[17,18]

We have analyzed a series of 452 cases treated with estrogens during the past seven years at the New York Hospital.[19] Most of these patients were treated by a similar regime, making them a relatively uniform group. Every precaution was taken to minimize factors which might predispose towards carcinogenesis. Prior to any treatment, thorough pelvic examinations were made and any inflammatory lesions found were corrected because of the relationship between chronic inflammation and carcinoma. Repeated gynecological check-ups of the state of the pelvis were made and the breasts carefully examined for the presence of nodules. The therapeutic use of the hormones was controlled by means of vaginal smears, permitting full replacement therapy to be achieved in most of the patients and the avoidance of excessive doses. No patient, therefore, received at one time more than would be equivalent to one human unit. This is far lower than the amounts needed to produce carcinoma in animal experiments. Thirdly, the estrogens were given with as short an interval as feasible between doses in order to avoid the irregularities of endometrial hyperplasia and regression which might be favorable conditions for neoplastic changes. In patients with an intact uterus, treatment was interrupted every four to six weeks to allow for a regression of the endometrial hyperplasia and to avoid a too prolonged stimulation.

An analysis of this group of 452 cases shows that at least in one

respect it fulfilled the conditions of the successful animal experiments, namely, a high tumor population. There were 82 cases of benign myomata of the uterus with removal prior to treatment, and one carcinoma of the fundus, also removed prior to treatment. Ninety-eight ovaries were removed, all benign; and there were nine mastectomies, three for malignant neoplasms. Of this group, one woman, who had a bilateral mastectomy in 1934 with the finding of an adenocarcinoma in one breast, developed metastatic lesions and a recurrence of the breast tumor four years after the original operation. She had received in this interval 3,000,000 I.U. of estrogen. The recurrence within this time does not warrant the conclusion that the estrogenic therapy was responsible. Otherwise the series was free of any instances of development of neoplasm. This, in conjunction with other studies cited, appears to offer no support for the view that the use of the estrogenic hormones in man is associated with the danger of neocarcinogenesis, provided therapy is carefully controlled in the manner indicated.

Results from Estrogenic Therapy in the Menopause

Since the signs and symptoms which present themselves at the menopausal age are part of a complex situation in which ovarian insufficiency is but one of the etiological factors, it becomes of importance to try to ascertain what effects may be expected from the use of hormones alone. In this way we obtain a better sense of proportion as to the significance of the whole set of changes at this life period. For those symptoms and signs which are not corrected by replacement therapy, other approaches must be sought or they must be accepted as inevitable consequences of the decrescent period of the life cycle.

The classical symptoms of the menopause, such as the vasomotor crises, headache, asthenia, insomnia, and the disturbances of peripheral circulation, may be expected to disappear at various levels of replacement therapy. Some of these, such as the hot flush, disappear more rapidly than others and are not too good subjective criteria on which to guide dosage. Pushing therapy to full replacement is the most certain method of determining the degree of well-being which can be experienced. No more gratifying restoration of health can be achieved in therapeutics than is so frequently seen in the menopause under adequate treatment.

Too much, however, must not be expected as regards many signs

and symptoms which accompany this syndrome but which are apparently part of a more fundamental alteration characteristic of this age period. One of the most troublesome complaints is that of joint pain involving particularly the knees, spine, and hands, and occasionally most of the other joints. It is an osteoarthritis of degenerative character, and seems to be specifically associated with the climacteric. Obesity tends to accentuate the difficulties. Hall[20] has reported considerable relief of these symptoms with estrogenic hormones. Our experience agrees with his in that, on the whole, the arthralgias are benefited. They may nevertheless persist, and frequently severely, despite intensive estrogenic therapy. They appear to belong to the group of degenerative changes in this age period the progress of which can be only partially influenced by ovarian hormone therapy.

There is some difference of opinion as to whether the hypertension so often seen at the menopause is specifically influenced by estrogenic therapy. Analysis of our results indicates that a well-stabilized hypertension is scarcely, or not at all, influenced by hormonal therapy. Where marked variations in blood pressure are encountered in association with emotional instability, the tension may be expected to be stabilized at the lower levels when estrogenic therapy has reduced the vasomotor instability and emotional tension. Nor does the obesity of this period seem to have any specific relation to the ovarian insufficiency. It should be dealt with by those measures which are employed at other ages, with, however, an avoidance of drastic procedures.

The anticipation that the estrogens would function as sex hormones in the sense that they would be able specifically to influence libido, has not been realized. There is a growing awareness that the sexual drive is grounded in more fundamental factors and that the concept that it was solely dependent on the reproductive secretions was an oversimplification of an extremely complex and subtle reaction. The changes in libido at the menopause are inconstant and to a large extent dependent on the intensity of the previous sexual drive and on the general discomfort attendant on the menopausal syndrome. The most that should be expected from replacement therapy is that libido be restored to its premenopausal level. The few instances where libido is increased are attributable to non-hormonal influences which enter the complex picture of this age period.

The psychic disturbances so prominent at this age period present an

involved picture which make it necessary to discriminate in terms of the character of the disturbance. The ability of a woman to survive the menopause without serious emotional disturbance is an indication of her previous emotional stability. A large proportion of the women who seek relief from menopausal symptoms have been maladjusted for a long time prior to the onset of the menopause. The majority of these women have presented psychoneurotic symptoms of the neurasthenic and hypochondriacal type. With the additional stress of the menopause these symptoms become accentuated. In addition, there are likely to be symptoms of anxiety and tension.

If there has not been serious maladjustment of the psychoneurotic type, the menopausal symptoms such as the depression and emotional instability are rather promptly relieved by hormonal replacement therapy. On the other hand, if the psychoneurotic maladjustment has been marked, there is usually only partial relief or relief of a temporary character, and some form of psychotherapy is necessary.

A smaller group of patients have more deeply seated problems such as may be noted in introverted or schizoid personalities. These patients tend to develop chronic hypochondriacal complaints, and sometimes the clinical syndrome of involutional melancholia. It would appear that, in the involutional cases, the menopause acts as a factor in precipitating a psychotic reaction which had for some time been latent and which represents a combination of personality problems for which there is no apparent solution. Feelings of guilt because of tabooed sexual thoughts or practices, or the resentment over the realization that the sex life is in part terminated, impose a burden to which the woman is unable to adjust.

An optimistic view with respect to the therapeutic benefit of estrogenic therapy in the psychotic reactions of the menopause has been expressed by several groups of workers, particularly Werner and his associates,[21] who have reported very favorable results with estrogens in involutional melancholia. Our more pessimistic attitude is based on a study of a small series of cases carried out with Ripley and Papanicolaou[22] in the Payne-Whitney Clinic of the New York Hospital. Of these, twenty were intensively studied for long periods. Seven were instances of involutional melancholia, six fell into the manic-depressive group, seven were milder reactions of a more reactive nature which may be classified as psychoneuroses of the depressive type. Full replace-

ment therapy, controlled by vaginal smears, with far larger doses than those employed in the previous studies cited was given for long periods during hospitalization.

Our general conclusions were that no specific effect on the psychosis could be expected from estrogenic therapy. Wherever associated menopausal symptoms contributed to the discomfort of the patient, these symptoms could be abolished. With this improvement in the general well-being of the patient came a somewhat better ability to cope with their problems, but this aid was of a non-specific character.

Problems Still Presented by the Menopausal Syndrome

Despite the gratifying progress that has been made in the treatment of the menopausal syndrome, many questions still remain unanswered. The situation is somewhat analogous to Graves' disease and diabetes mellitus where a therapeutic measure of considerable effectiveness still leaves unsolved many of the primary problems relating to the genesis of the disease.

Of the questions still awaiting solution, one may be singled out for brief comment in concluding this survey because of my growing conviction that it may reach to the heart of the problem. Our therapeutic successes should not cause us to lose sight of the fact that we have no knowledge of the cause of the menopausal syndrome. We believe that it represents a failure to adjust to the new internal environment which follows the cessation of ovarian function; but why this occurs in one group of women and not in the other remains obscure. When one studies the menopausal syndrome from the broader aspects of the evolution of the total personality, it becomes increasingly apparent that here as well as in Graves' disease, psychogenic factors may play a very important, if not primary, role in preventing an adjustment to the new status. One sees instances in which the adjustment to the menopause had taken place smoothly years before, and where acute and distressing symptoms suddenly arose years afterwards in association with some emotional stress. One sees relief of menopausal symptoms following therapy with an apparent satisfactory adjustment suddenly interrupted by a renewal of all the old complaints in their original intensity under the influence of some new psychic strain. The importance of psychic influence is also commonly seen in the greater resistance of the severely psychoneurotic menopausal patient not only to the subjective but to

the biological effects of estrogenic hormones.

The implications of these observations for the direction of our future approach to the study of the problem of the menopause are apparent. The sooner we learn to regard the menopausal syndrome not as an entity but as a symptom of a more fundamental psychobiological maladjustment, the more rapid will be the attainment of our eventual therapeutic goal, its prophylaxis.

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CLINICAL ASPECTS OF RHEUMATIC FEVER IN CHILDREN*

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IT WOULD be presumptuous on my part to recite the manifest symptoms which we associate with rheumatic infection in children. These are well known to all of you. It is a subject too vast to cover adequately in the short time allotted to me. Suffice it to say that this disease is a scourge of childhood, and takes a heavy toll in the first two decades of life. That the New York Heart Association should see fit to devote an entire evening to its consideration is significant and important. Rather, would I attempt to point out some of the minor patterns of rheumatism in children which are less frequently recognized. The alert physician should make at least a presumptive diagnosis in the subclinical phase of the disease, and should avail himself of the laboratory tests to supplement his clinical observation. The child who tires easily, who unaccountably is losing weight, has a poor appetite, is becoming more pale, and has indefinite muscle pains, should arouse the suspicions of the physician and a careful survey and appraisal should be made. Mild types of chorea may be overlooked, and the physician should be on the alert, in the knowledge that even mild chorea may induce carditis of a severe degree. A low grade fever may be discovered, and the erythrocytes may sediment more rapidly than normal. These are minor patterns of the disease in its early stages.

We too often err in thinking that rheumatism and joint infection are synonymous. Polyarthritis, associated with rheumatism, is not nearly as frequent in childhood as it is in later life. We should get away from this concept, and be more alert in the early recognition of the disease. I am more and more impressed with the absence of joint symptoms in many of these rheumatic children, particularly in the early years. McIntosh and Wood reported twenty-four children at the Babies Hospital who developed the disease before three years of age. Less than half

* Read March 26, 1940 at The New York Academy of Medicine at the meeting of the New York Heart Association.

of these gave a history of having had joint symptoms. Ninety-six per cent exhibited either clinically or pathologically rheumatic heart disease. The youngest case was twenty months of age.

We hear much about "growing pains" in children. That these occur in the absence of rheumatic infection is unquestioned. The physician is often puzzled to differentiate the rheumatic from the non-rheumatic pains. It is here that laboratory aid must be sought. The observation of Hawksley in England and of Shapiro in this country at a meeting of the American Rheumatism Association would indicate that growing pains are not uncommon in healthy growing children, and that a very small per cent develop rheumatic carditis. An interesting explanation has been given by Erdheim, that in certain rapidly growing children, minute fractures of the metaphyseal plate occur. He has demonstrated these minute fractures at the growing ends of the long bones in children who have died of acute illness or by accident. This is, by far, the most satisfactory explanation of "growing pains" that I know. To my knowledge there has been no report of this in the English literature. On the other hand, we do see children suffering from severe carditis with no other history than that of "growing pains." The differential diagnosis should be made, or at least suspected, so that prompt treatment may be instituted. Where rheumatism is suspected, such laboratory aids as the electrocardiogram, the sedimentation rate, the white blood count, and the Addis count in the urine, may be helpful. I have had no experience with the Weltmann sero-coagulation reaction as a non-specific test. This needs to be further evaluated. At present the erythrocyte sedimentation rate is probably the most valuable single blood study in rheumatic infection. It needs no elaborate apparatus nor laborious technique. It is therefore important to differentiate "growing pains," not only from the standpoint of the child, but also in the study of the problems of rheumatism. Partial invalidism and institutional care may thus be prevented in a group of children who are erroneously diagnosed as having rheumatic infection.

Abdominal pain may occur in the rheumatic state, and may be so acute as to simulate other surgical conditions, notably appendicitis. Some years ago we reported an appendectomy performed on an eleven year old negro boy who, a few days later, with a persistence of the fever and a rapid sedimentation rate, developed polyarthritis, an erythema marginatum, and evidence of carditis. In this case the pathologist made

a presumptive diagnosis, and on his report asked, "any evidence of rheumatism?" The pain, in this case, was probably only partly due to the appendix. It is more than likely that the greater part of the pain was due to an invasion of the peritoneum, or a periarteritis involving the mesenteric vessels. It is well to note that abdominal pain may be a pattern in the rheumatic picture, and often will confuse the clinician in the determination of its cause. Obviously it is important to do so.

Over a period of eighteen years it has been my privilege to have had an opportunity to observe over long periods of time in three cardiac homes near New York a large group of children afflicted with rheumatic heart disease. We (I use the word "we" advisedly, for there have been many individuals concerned in this study, and without their arduous labors, loyalty and enthusiasm, this work could not have been possible) have cared for, under as ideal conditions as it is possible to attain in a convalescent home, some 1,378 children. Seventy-nine of these were drawn last year from some thirty-one cardiac clinics in the five Boroughs of New York City. This group of children, at the time of their admission to these Homes, by all the known criteria and laboratory tests, have been in the quiescent stage of their infection. However, even under ideal living conditions, reinfections do occur, and often necessitate a return of the child to the hospital from which he came. This is a discouraging feature of the work, but there are many encouraging ones; 962, or 70 per cent of these children are living, and the majority leading useful lives. One hundred and eleven have been married, and eighty-six children have been born of these marriages. Since children are accepted only when there is not a predominating throat culture for beta-hemolytic streptococci, recrudescences are less than was formerly the case. We find that these reactivations are preceded as a rule by an upper respiratory infection some two weeks prior to the onset. The child complains of a sore throat, and there is a sharp rise in fever which subsides in two or three days. This is Phase 1 of the 3 Phases which Coburn and Pauli have described in the evolution of rheumatic fever. Then follows Phase 2 of about two weeks, which is afebrile and symptom free. Then Phase 3 ensues. This is the period of acute rheumatic symptoms. Coburn and Pauli state that Phase 2, the afebrile stage, is "the crucial stage in the genesis of rheumatic symptoms." They have demonstrated in this Phase 2 a diminution in serum complement, which becomes further reduced during Phase 3. In commenting on their

work, the Journal of the American Medical Association says editorially that "since decreases in serum complement are known to take place when antigen and antibody coexist in the circulation, Coburn and Pauli postulate the existence of a Phase 2 pre-rheumatic antigen, reacting with a Phase 3 antibody as a cause of this complement 'deviation.' The demonstration of secondary antigens and antibodies in rheumatic fever is clinical confirmation of a speculative hypothesis proposed a decade or more ago by immunologists. If confirmed, this renaissance of the speculative theory of secondary anaphylaxis and immunity may lead to practical diagnostic and therapeutic methods in numerous infectious diseases."

What I want to point out is that these reactivations are unpredictable in any given child and are often bizarre in their manifestations. They often present no symptoms or signs except a low grade fever and accelerated heart action. The late Lucy Porter Sutton stressed so often gallop rhythm as an important sign of activity. In an institution these children with reactivity and active carditis may be discovered in their subclinical phase by laboratory aids, but one wonders how many are running the streets and even attending school with few if any symptoms, and yet in the active phase of the disease. You can thus see why it is so difficult to determine what constitutes a reactivity in the follow-up of these children, and what makes the whole problem of rheumatic infection such a prodigious one. Monocyclic types of rheumatic fever are not common in children. The questions arise: "What criteria can we apply to determine reactivation?"; "when does infection end and convalescence begin?"; "why does one child have but one bout of rheumatic fever and another (perhaps a brother or sister) have five or six bouts?" Added knowledge each year is helping to answer these perplexing questions.

As this meeting is planned to promote an educational campaign in the interests of rheumatic fever, a few words should be spoken about this disease as a public health problem. The morbidity and mortality figures of rheumatic heart disease are staggering. The incidence in this country is conservatively set at about 800,000 to 1,000,000 individuals, and the mortality about 40,000 deaths each year, with the average age at death, thirty years. Until rheumatic fever is made a reportable disease we will have no accurate data. Why the Public Health Services and Departments of Health have not seen fit to do this is hard to under-

stand. The incidence of rheumatic valvular lesions in children is about 1 per cent of the school population. This would mean that about 10,000 school children in New York City are so afflicted. As they grow up these make up the greater number of adult cardiacs in the second and third decades.

But the morbidity of rheumatic heart disease is overshadowed by the high mortality. Our figures indicate a mortality rate of 30 per cent in the group of 1,378 children followed for 18 years, that is 416 deaths. This has risen from a figure of 28.7 per cent in 1938. We have found that over half of these 416 deaths have occurred within the first five years of their initial infection. This coincides with Duckett Jones' observation of 1,000 children with rheumatic carditis. Two-thirds of those dying have died within 5 years of their primary infection. Duckett Jones' 10-year follow-up on 1,000 rheumatics shows a 25 per cent mortality. Stroud's recent 15-year follow-up on 685 children reports a mortality rate of 21 per cent. Death is not common in the first attack, but occurs more often in the second or third attack. From this it is quite obvious that the most important time in the life of the rheumatic child is the first five or six years following the initial infection. This occurs usually between five and twelve years of age, the average age being seven years. The brunt of our attack on this dread foe of childhood then must be during these all important years following the primary invasion. It is well to interpolate here that most of these children die of their infection and not of congestive heart failure, as is more common in the young adult cardiac.

From what we know concerning the devastating effects of rheumatic fever is it not evident that this disease has become a public health problem of major importance? It becomes our concern. In the first place, in our own State of New York, the term "cripple" should be broadened so as to include the child with rheumatic heart disease. Howard Haggard of Yale University has coined the phrase "Crippled children who do not limp." The American Academy of Pediatrics has put itself on record in the cause of children so crippled with rheumatic carditis. It is difficult for the lay person to visualize a child with a damaged heart as a cripple or as handicapped. The boy or girl may not look ill, but in spite of this, his or her activity may be greatly curtailed, and the games and sports of normal children denied. Too often the span of life is shortened. Our figures show that 363 or 87.7 per cent of the

total 416 deaths have occurred before the age of 20 years. The orthopedic cripple, or the child crippled by infantile paralysis, arouses our sympathy, and justly so, but when one considers that rheumatism destroys seven times as many children as does anterior poliomyelitis, then you have some conception of the ravages of the disease. In one sense, the child stricken with infantile paralysis is more fortunate than the child stricken with rheumatism. The latter confers little if any immunity, and reactivations occur all too frequently. In fact they are more often the rule than the exception. Each one adds still further injury to a heart already damaged. On the other hand, infantile paralysis, as dread a disease as it is, usually confers an immunity to subsequent attacks and the afflicted child may anticipate varying degrees of return of function. To quote from a recent article, "a child with a withered leg can see his own infirmity, and seeing it, understand it. A child with a crippled heart cannot see his injury; he must be told, and, having been told, believe it. He must suit his life to an intangible infirmity that imposes its limitations on all of his physical activities."

Many children who contract infantile paralysis recover completely with no resultant paralyses or crippling. Very few children who contract rheumatism escape without some damage to the heart of greater or less degree.

It is my hope that an educational campaign in the cause of rheumatism may be extended and organized on a par with the infantile paralysis, tuberculosis and cancer campaigns. From the standpoints of total mortality and age at death it ranks as one of our major health problems. At this time, when the Children's Bureau in Washington has embarked on a program for the care of the child crippled with rheumatic heart disease, it would seem that "now is the accepted time" to mobilize all individuals and health agencies interested in this problem. I hope that this meeting tonight, and the annual meeting of the New York Tuberculosis and Health Association just three weeks ago, to which the New York Heart Association contributed, may provide the stimulus to initiate such a campaign of education in the interests of these crippled children, adolescents and young adults. The President, speaking on the scourge of infantile paralysis a few weeks ago, said: "As the years go on, I hope that the task will be extended to care for all crippled children, no matter what the cause of their crippling."

There is an urgent need for more beds, first, for sanitorial care,

comparable with London's 1,100 beds, and, second, for the convalescent child in the quiescent stage of the disease. Only 500 beds for convalescent care are available in this country, of which nearly 300 are in the vicinity of New York City. Such a provision would allow for prolonged bed rest which is so necessary. Long bed rest would seem just as advisable in this disease as in tuberculosis. It is well to note that about 66 per cent of these children are discharged from the acute hospital after an average of only one month's care; and the majority return to homes of poverty, want and bad hygienic surroundings. Is it any wonder that reactivations occur, and that so many succumb to their infection?

I cannot end this paper without a word concerning the larger problem of the child who is crippled with rheumatic heart disease. We must not forget that there is not only the heart to be treated, but there is also the child who has the heart. In other words, attention to the *psyche* is quite as important as attention to the *soma*, and may be even more so. There should be an integration of this psychosomatic relationship. The physician should have an awareness of the child as a whole, and should realize that the handicapped child has a greater need for help and adjustment than the normal child. Psychiatric counsel should be sought and should implement the therapeutic approach to the child with rheumatic heart disease. There are educational, social and emotional factors in the life of these children which require, often, the help of one trained in child psychiatry. This is an area in the care of the cardiac child which has been woefully neglected. It is an aspect which was stressed at the two-day conference on Convalescence last fall held in this building.

Too many children labelled cardiacs are being carried in clinics or taken care of by private physicians without justification. They are condemned to a life of partial invalidism merely because of a cardiac murmur. This is indefensible. How easy it is to develop an "invalid reaction" which later may become a neurosis, with feelings of insecurity, inferiority and anxiety. In my opinion, one of the most important functions of the cardiac clinic is to weed out these children who are stamped as cardiacs, but who have no organic disease of the heart. In doubtful cases I would prefer to take a chance with certain of these children rather than subject them to a life of partial invalidism with its train of psychic maladjustments.

I wish there were time to speak of the social service, and the vital role which the trained social worker plays in the total care of these

children. She is an important link in their guidance and rehabilitation. I know of no more important social work than this.

In conclusion, to those of you who were not fortunate enough to hear the John Wyckoff Memorial Lectures given by Dr. Swift a short time ago, I would commend them for your reading and study. They constitute the most thorough exposition on rheumatic fever that I know of. They will fill in the many gaps of this presentation.

PURPOSES, FUNCTION AND USE OF STANDARD CLASSIFIED NOMENCLATURE OF DISEASE*

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THE Standard Classified Nomenclature of Disease is now employed in almost all important hospitals and medical schools of the United States and Canada. Several years ago I found it in use in many of the large hospitals of London. At the meeting of the International Commission held in Paris in October 1938 for the purpose of preparing the decennial revision of the International List of the Causes of Death, it was the only reference work which the British delegation brought into the conference room as their standard authority on medical nomenclature.

The success of this American enterprise is largely due to the manner in which it was prepared during the years preceding the publication of the first edition (1928-1933). It was initiated and carried through to completion by a nationwide collaboration of all the important national societies representing medicine, surgery and the various specialties. It is to the credit of The New York Academy of Medicine that the Academy issued the first call to the conference of national societies just twelve years ago. When the national conference on Nomenclature of Disease was organized in response to this call, the Academy withdrew officially from participation, because as a local organization it had no place in a national body, if the nomenclature to be created was to be acceptable as authoritative throughout the United States and Canada. However, it continued to aid in obtaining the necessary financial support from various philanthropic foundations and insurance companies and provided office space for seven years.

Previously, there had been hundreds of local efforts, the best known being the Bellevue, the Massachusetts General, the Presbyterian, the Ponton, some named after hospitals, others after their authors. Increasing numbers led to increasing perplexity on the part of hospital administrators and clinicians. As they multiplied in number and variety, their

* Read March 1, 1940 before the National Conference on Medical Nomenclature of The American Medical Association, Chicago.

many authors failed to appreciate the fact that they were modifications of preëxisting efforts which merely perpetrated illogical and overlapping methods of classification; that each was colored by peculiarly local hospital needs; and that in their separate parts they did not express the ideas or meet the demands of advanced experts in the highly specialized branches of medicine and surgery.

The purpose of a nomenclature is to encourage the use of expressive terms, the meaning of which can be accepted universally without ambiguity. The best term is the one which most completely expresses the nature of the disease. The names of discoverers of disease are generally unsatisfactory synonyms, are often the subject of dispute in various countries and sometimes even in different sections of the same country. Although Latin may be permissible for the generic classification of bacteria, the descriptive terms employed for the diseases should be expressed in English. As in the Middle Ages, Latin still serves to obscure the true depths of ignorance. This form of medical obscurantism lingers on in some of the more backward fields of medicine.

The primary purpose of a *classified* nomenclature is to arrange the diseases in a logical and orderly manner so that there may be no possibility of overlapping one another. This is important for accurate keeping of records in the disease file of a hospital record room. Now that almost all important hospitals use the Standard Classified Nomenclature, the disease files of their record rooms are mutually interchangeable. Their clinical experiences are readily available for study as well as for comparison with the experiences of other institutions.

The chief virtue of the Standard Classified Nomenclature of Disease is that from beginning to end it never departs from the simple construction of its basic schema. Every disease is described and classified topographically, in terms of the tissue or organ where it is principally manifested, and also into etiological categories. This has permitted the use of a simple library decimal system which greatly facilitates record room filing. The numerical designations on each side of the dash, often describe topography and etiology more accurately than the traditional name of the disease.

There has been some complaint that the six or more numbers necessary to designate a disease or injury do not lend themselves as readily for punch card recording as some simpler numerical systems. It must be remembered that the primary purpose of the Standard Nomenclature is

for clinical use. It is to encourage uniformity and accuracy in clinical expression. Our dual decimal system for the numerical designation of the diseases permits the employment of the Standard Classified Nomenclature of Disease as a clinical discipline, not only for fourth year medical students who as clinical clerks are being taught to think and to express themselves accurately and completely, but also often as a much needed clinical discipline for the attending staff of the hospital. Rebel at first, as they will, they soon learn to write their diagnoses in completely descriptive terms which can be filed by the record room clerk. "Contracted kidney" is not an acceptable term and cannot be filed unless the clinician describes the condition more completely as chronic glomerulonephritis, pyelonephritis, arteriolar nephrosclerosis, hydronephrosis, or congenital hypoplasia. If the clinician cannot make a complete diagnosis, that fact can also be recorded accurately. The record room must invariably know the complete diagnosis if it is available. If the clinician is dealing with a case of acute bacterial endocarditis or a case of poisoning, he must name the bacterium or the poison before the diagnosis can be filed or else he must state specifically that the cause was not determined.

In order to encourage the use of the Standard Nomenclature, many hospitals have purchased a copy for every ward and have chained the volume to each ward desk so that it is always available to the clinician when he is inscribing the final diagnosis on the patient's discharge card or on the clinical record.

The resistance of clinicians to making the little extra effort required by the use of the Standard Nomenclature is soon replaced by appreciation of an orderly disease file in the hospital record room. Medical students who have been subjected in the fourth year to the discipline of the Standard Nomenclature make better interns. We have reason to hope that the coming generation of practicing physicians who have come under its influence as students and interns will have developed the habit of thinking and speaking in more concise medical terms. No one will appreciate this more, I am sure, than the overburdened editor of the Journal of the American Medical Association.

Perhaps this was one of the reasons why I found no resistance on the part of Dr. Fishbein and the trustees of the American Medical Association when in 1937 on behalf of the National Conference I proposed to turn over to the Association the permanent responsibility for

the Nomenclature. This responsibility belongs rightly in the American Medical Association but in effecting the transfer, the hope was expressed at the time that the Association would continue to work through the medium of a National Conference, composed of all the national clinical societies, the Federal medical services and other interested organizations. By this nationwide collaboration the Standard Classified Nomenclature of Disease will continue to serve all the physicians and hospitals of the country as their authoritative guide on matters of diagnostic terminology.

Suggestions continue to be advanced that the Standard Classified Nomenclature of Disease is too large. We have given much thought to this matter of size. Physicians, whether in small or large hospitals, expect to find every disease term in a reference work of this nature. A significant abbreviation of the book can only be accomplished by omitting thousands of diseases of rarer occurrence and the volume would then lose its value even for small hospitals. The size of the volume and the number of terms it contains does not complicate the problems of the record room clerk or of the hospital physicians. In fact, the completeness of the nomenclature simplifies their work, for in the index or in the text they will find every known disease and in the basic schema there is a place reserved for every disease that is still unknown. The size and complexity of the disease file of a record room is not determined by the size of the Standard Nomenclature. In institutions, large or small, the disease file will only contain a record of those diseases which have been encountered in the hospital's own clinical experience.

As has been suggested by Dr. Edwin P. Jordan, the number of pages in the volume may be reduced by omitting certain common conditions which recur frequently in many parts of the body, such as abscess. The physician can combine the term "abscess" with any tissue or organ of the body and he or the record room clerk can then find the appropriate topographical code number by consulting the classification schema (pp. 17 to 58) and adding the etiological numerical designation for abscess and for the infecting agent. It would still be necessary to include some of the more common forms of abscess in the text, such as subphrenic abscess, abscess of the lung.

Surprising though it may seem, there are some who think the Standard Nomenclature is not large enough and who demand an opportunity to record various clinical manifestations of disease or even laboratory

findings. This is beyond the scope of a nomenclature of disease. No two institutions and no two men in the same institution can agree upon which symptoms of disease and which laboratory findings are worth recording in a disease file, and the same physician often changes his own opinion from year to year. Symptoms and laboratory findings are included in the complete clinical record of each case, and every clinical research requires a restudy of all the clinical records. To attempt to record such data in the disease file by means of supplementary code numbers is an unnecessary complication. Furthermore, it is usually inaccurate and undependable because of inconsistencies on the part of the clinical staff. Whenever an authoritative national specialist society such as the American Heart Association or the American Neurological Association has agreed officially upon the desirability of recording such specialized information under a supplementary system of coding, the list has been included in the volume.

A criticism of the Nomenclature is that it does not lend itself readily to cross reference to the rubrics of the International List of the Causes of Death. After each disease, the appropriate code number of the international list is to be found. This can be transferred to punch cards for statistical tabulation. In this manner morbidity can be compared statistically with mortality information.

Another criticism is that the Standard Nomenclature cannot conveniently be used for the statistical tabulation of summary reports on hospital morbidity. It must be remembered that the Nomenclature is designed primarily for clinicians, for the diagnoses as they make them are the sources of information concerning the prevalence and distribution of disease.

If group tabulations are desired, an abbreviated tabular list must be adopted for duplicate recording on punch cards. The tabular list may follow the disease arrangement of the international list of the causes of death so as to facilitate comparison of morbidity with mortality information. This was done successfully in the recent WPA study of the diagnoses of patients discharged from New York City hospitals. The difficulty in agreeing upon a tabular list for simplified statistical recording is that the information which is to be summarized statistically must differ radically if it is designed for hospital administrative purposes or for public health work. Such abbreviated statistical summaries seldom have any value for clinicians. A clinician is better served by

obtaining the specific information which he may desire directly from a complete hospital disease file which is properly classified for clinical purposes in accordance with the Standard Nomenclature.

Although this third edition of the Standard Classified Nomenclature of Disease may not require revision for five years, a central staff must continue to be maintained as the clearing house for the exchange of opinions on the use and the significance of both new and old diagnostic terms. Although the editorial influence of the Journal of the American Medical Association has long set a standard for the United States, the services which the assistant editor, Dr. Jordan, has rendered to the hospitals and the clinicians of the country in hundreds of details must be continued if nationwide collaboration is to be maintained.

THE ADAPTATION OF THE STANDARD CLASSIFIED NOMENCLATURE OF DISEASE TO HOSPITAL MORBIDITY REPORTS*

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HOSPITAL-SICKNESS experience is of interest not only to the medical and administrative personnel of each particular institution, but also to the community at large. Whether it be for the particular purpose of a single institution or from the broader community viewpoint, it is the mass aspect of the material rather than the minutiae that is of importance. It is the mass aspect of the statistical approach that gives it validity, in contradistinction to the minutiae of each particular case which are the sine qua non of the individual clinical study. It is only from the study of bulk phenomena that certain tendencies or perspectives become discernible. Among the important deductions from the study by W. J. Mayo[1] of 10,280 operations performed at St. Mary's Hospital, Rochester, Minn., was the statement that "some deaths and many poor end results occur with a regularity so definite that their incidence can be foretold from year to year." Only individual case studies can prevent the recurrence of particular untoward events. Many years ago, Frederick L. Hoffman[2] of the Prudential Life Insurance Company, in a special monograph, outlined the many significant facts which can be obtained from hospital experience. This study was based on the statistical data of Johns Hopkins Hospital from 1892 to 1911.

The experience of a single hospital gains much in significance when compared with that of other similar institutions. To make such comparisons valid there must be some agreement between hospital authorities as to common fundamental categories and as to terms. From the outset it should be recognized that mass statistics of hospital experience are of no clinical value or, at best, very limited clinical value; that scientific statistical studies of selected clinical conditions have no place in a hospital report and are beyond the scope of morbidity statistics.

* Read March 1, 1940 at the National Conference on Medical Nomenclature, Chicago.

The compass of this paper precludes a detailed discussion of the value of morbidity statistics in general and of those of the hospitals in particular. This has been covered extensively in many other writings. The need of a systematic collection of morbidity data from various sources has, I believe, been well established.[3] Granted that such body of information is needed for civic, biosocial, pathometric, demographic, and actuarial purposes, the question is how should such a body of information be obtained and systematized and what part hospital experience should play in it.

For the moment, it is the latter or the hospital experience that is of particular moment and that only in its nosological relationships. Because, however, of the extensive use that has been made of mortality statistics in the discussions of incidence of disease, it may not be amiss to emphasize that death statistics, even when they are based on accurate certifications, give only a partial account of illness, for in the published tabulations only the principal or final cause of death is recorded and the contributory causes are omitted. These contributory conditions are often of socially greater importance than the terminal cause. Furthermore, to base the knowledge of the prevalence of illness on mortality bills, is often misleading. Ratios between morbidity and mortality in each disease are never constant. These ratios change not only with the varying virulence of the causative organism, if the disease is of germ or virus etiology, but also with the age distribution of the population of a given community, the economic environment and the existence or non-existence of medical institutions and their adequacy or inadequacy. Hence, generalizing with regard to morbidity on the basis of mortality is hazardous and may be utterly misleading.

In the foregoing paragraphs an attempt has been made to emphasize the need for hospital morbidity statistics apart from mortality statistics, and to indicate that such statistics are of service to the hospitals themselves and to the community at large. Now, as to the modus operandi. The experience of the Peter Bent Brigham Hospital, the Mayo Clinic, the Johns Hopkins Hospital, and some other individual efforts, is no doubt of much value. So also is the experience of three attempts in New York City at collective gathering of hospital data. Other communities may likewise have attempted the pooling of hospital morbidity data; in that event the base of experience is still broader. The first demonstration of the kind was made in New York under the direction of the Hospital Information and Service Bureau of the United Hospital Fund in 1923 in

coöperation with six hospitals.[4] In this experiment the simple method suggested by Bolduan[5] was followed. The participating hospitals agreed to send certain information concerning their discharged patients, using a form of certificate agreed upon, and these certificates were edited by a medical registrar in the same way as death certificates are registered by a registrar of vital statistics. There was no uniformity in the manner in which diagnoses or other data were reported from the coöperating hospitals. The second study on a much larger scale was that undertaken under a large WPA grant by the Research Division of the Welfare Council of New York City. It covered the entire annual experience of 113 hospitals in 1933 and comprised data pertaining to approximately 576,000 patients.* Here again there was no uniformity in the reported facts and, as in the former study, a method of procedure had to be worked out to make possible a practical approach to the problem of classification. One of the valuable results of this experiment is the "Classified List of Diagnoses for Hospital Morbidity Reporting"[6] published by the Welfare Council of New York City. This is based roughly upon the Standard Classified Nomenclature of Disease, although the arrangement of the group diagnoses followed the International List of Causes of Death as far as possible. The third experiment is that which has been carried on for the last ten years by the Division of Medical Records and Statistics of the Department of Hospitals since 1929, when all the municipal hospitals in the City were consolidated into one department. The work of that Division under Caroline Martin is no doubt the most outstanding contribution in the field of hospital morbidity statistics, due to the remarkable ingenuity and competence of its direction and because of the insignificant cost of the enterprise.

Only recently has the Standard Classified Nomenclature been introduced in all the municipal hospitals and this has, no doubt, simplified the task of the central statistical office. Irrespective of the number of group classifications into which an abridged list must be divided, it is easier to use the individual entries of the Standard Classified Nomenclature than those of any other list, first because they are precise, and second because the scientific system of nosology developed in the Standard list has gained widespread approval and will no doubt become universal in time. If it should be advantageous to correlate the groupings of combined entries with the International List of Causes of Death, a method of cross-

* This study has not been published as yet, except for a monograph describing the method used.

reference can be worked out which will serve the purpose. It is to be regretted that the Mayo Clinic Tabular Outline has been based entirely on the International Causes of Death, with such additions as were considered of importance from a pathometric or biosocial viewpoint.[7] Some of the items in that list could be omitted with benefit. There is no need in a hospital morbidity list of special entries for torticollis or for menopause or cretinism or idiocy and many other conditions rarely encountered in general hospitals. Whenever possible, the use of eponyms in any list should be discouraged on general principles. The Welfare Council list, though much shorter than that of Mayo Clinic, provides entries for numerically important conditions which are lumped in the Mayo Clinic outline, such for example as detachment of retina, strabismus, ulcer of the cornea, and other diseases of the ophthalmic system. On the other hand, the shortcoming of the Welfare Council grouping lies in the fact that it follows neither the International List nor the Standard Classified Nomenclature. Only five of the groupings in that list are based on the principle of etiology; the others refer to symptomatology or anatomical site. This may have been due to the need for tabulating poorly recorded information. Until the Standard Classified Nomenclature becomes generally used, a compromise arrangement may have to be used. It should, however, be pragmatically useful and should be generally agreed upon, as otherwise no valid comparisons are possible.

The four considerations followed in the tabulation of the material by the Welfare Council of New York City should be critically reviewed and such changes suggested as may be most acceptable for general adoption. The four guiding principles in the arrangement of the material in the Welfare Council classification were:

1. Elimination of superfluous diagnostic notations. In the actual tabulation of the 576,000 hospital discharge records, a single diagnosis was chosen for 78 per cent of the cases, two diagnoses were entered in 17 per cent, three diagnoses in 4 per cent, and in only 1 per cent of the cases were four diagnoses tabulated.

2. The discarding of complicating conditions which accompany the major condition or of typically secondary conditions.

3. The placement of several manifestations of the same etiology under one diagnostic designation.

4. Elimination of accessory conditions which are accidental and have no relation to the disease for which the patient was hospitalized.[8]

Neither the Mayo Clinic nor the Welfare Council classification lists surgical operations. From an administrative as well as a social viewpoint it is desirable that hospital reports include a classification of operations, prepared in accordance with some uniform, agreed upon method. The one used by the Division of Records and Statistics in the Department of Hospitals of New York City has proved of practical usefulness.

There are numerous other tabulations of administrative value which should be prepared and correlated with the medical and surgical experience of the hospitals, such as: total days' stay; mortality, although this is always of questionable value; occupations; and seasonal cycle. These and other important items do not come perhaps within the purport of discussion of this particular conference. I wish, therefore, to conclude with emphasis on several points in relation to hospital morbidity statistics:

First, the value of such statistics to hospital administration, to demography, to community planning, and to social insurance.

Second, the desirability of a uniform classification of hospital morbidity and of surgical operations for comparative purposes.

Third, the recognition of the fact that mass hospital statistics are of limited value from a clinical viewpoint, and that they are scientific only when they are carefully prepared and correlated in accordance with certain agreed upon principles of sound statistical procedure.

Fourth, the availability of the Standard Classified Nomenclature is a factor in making such tabulations easily referable to accurate clinical entries and simplifies the work of coding.

Fifth, hospital morbidity statistics should be prepared in close conformity with the International List of Causes of Death, because of convenience and cross-reference.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

MAY 2—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Presentation of certificates of fellowship. ¶ Papers of the evening—Problems of aging—a] The general problem, George Morris Piersol, Professor of Medicine and Vice Dean for Medicine, University of Pennsylvania, Graduate School of Medicine; b] Cardiovascular, Ernst P. Boas, Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; c] Neuropsychiatric, Foster Kennedy, Professor of Clinical Neurology, Cornell University Medical College. ¶ Report on election of Fellows.

MAY 16—*The Harvey Society (in affiliation with The New York Academy of Medi-*

cine) The Eighth Harvey Lecture, "The Chemical Composition of the Lipoids of the Tubercle Bacillus," R. J. Anderson, Professor of Chemistry, Yale University.

SECTION MEETINGS

MAY 3—*Section of Surgery.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, Grant P. Pennoyer; for Secretary, Frank Brown Berry; for member of Advisory Committee, J. William Hinton. ¶ Presentation of cases—a] Tetanus following acute suppurative appendicitis with recovery, R. Sterling Mueller. Discussion, Seward Erdman; b] Mesenteric thrombosis with resection of small bowel. Result after two years. Traumatic rupture of the retroperitoneal portion of the duodenum, Caldwell B. Esselstyn. Discussion, Leon Ginzburg; c] Cases of subphrenic abscess illustrating paper of the evening, Abraham Jacob Beller. ¶ Papers of the evening—a] Subphrenic abscess with report of five cases, Abraham Jacob Beller. Discussion, John H. Garlock; b] Drainage of pelvic abscess through the rectal wall, Howard A. Patterson. Discussion, Paul C. Morton; c] Appendiceal abscess. Management and review of 100 cases, Edward Victor Denneen. Discussion, Charles Gordon Heyd. ¶ General discussion.

MAY 7—*Section of Dermatology and Syphilology.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, George C. Andrews; for Secretary, Herman Sharlit; for member of Advisory Committee, Louis Chargin. ¶ Presentation of cases—a] Cases from hospitals of Brooklyn; b] Beth Israel Hospital; c] Sea View Hospital; d] Miscellaneous cases. ¶ General discussion.

MAY 7—*Combined Meeting New York Neurological Society and Section of Neurology and Psychiatry.* Executive session—Section of Neurology, Psychiatry. Election of Section Officers and member of Advisory Committee—for Chairman, Samuel Brock; for Secretary, George H. Hyslop; for member of Advisory Committee, Lewis D. Stevenson. ¶ Papers of the evening—a] Periodic dullness as an epileptic equivalent, H. H. Merritt (Boston), (by invitation), Tracy J. Putnam. Discussion, Richard M. Brickner; b] Electro-encephalographic localization of focal cerebral lesions, Herbert Jasper, D.Sc. (Montreal), (by invitation). Discussion, Leo M. Davidoff; c] The repetitive core of neurosis, Lawrence S. Kubie. Discussion, Bertram D. Lewin.

MAY 8—*Section of Historical and Cultural Medicine.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee — for Chairman, Ramsay Spillman; for Secretary, Claude E. Heaton; for member of Advisory Committee, Louis Casamajor. ¶ Papers of the evening—a] Giuseppe Zambeccari—a Seventeenth-Century Pioneer in experimental surgery, Saul Jarcho (by invitation). Discussion, Allen O. Whipple; b] Treatment of mental disorders in France at the end of the Eighteenth Century, C. P. Oberndorf. Discussion, A. A. Brill, Leland E. Hinsie.

MAY 9—*Section of Pediatrics.* Case demonstrations from 7:30 to 8:00 o'clock. ¶ Executive Session. Election of Section Officers and member of Advisory Committee—for Chairman, Leslie O. Ashton; for Secretary, Alfred G. Langmann; for member of Advisory Committee, Rustin McIntosh. ¶ Presentation of case reports—a] Roosevelt Hospital—Spherocytic jaundice with splenectomy in a five-months' old infant, Alexander T. Martin and James E. Thompson; b] Lenox Hill Hospital—A case of essential hypertension and precocious puberty, Irwin Philip Sobel; c] New York Post-Graduate Hospital—A case of Ehler-Danlos syndrome, George E. Pittinos

(by invitation); d] St. Luke's Hospital — Osteogenesis imperfecta — Lobstein type, Elizabeth B. Hinckley (by invitation); e] Polyclinic Hospital—Encephalitis following smallpox vaccination, Benjamin Roman (by invitation); f] Willard Parker Hospital — Guillain-Barre syndrome, Samuel Spector (by invitation); g] The Mount Sinai Hospital—Lymphocytic meningitis (2 cases), H. Kaufman (by invitation); h] Harlem Hospital—A case of scurvy with interesting roentgenograms, Harry J. Cohen (by invitation); j] Knickerbocker Hospital—Pneumonia in twins: Type I pneumococcus pneumonia involving identical lobes in identical twins, Lewis Jacobs (by invitation).

MAY 15—*Section of Otolaryngology.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, James W. Babcock; for Secretary, Page Northington; for member of Advisory Committee, Jacob L. Maybaum. ¶ Case reports—a] Otitic tetanus, Samuel Rosen; b] Thrombophlebitis of the cavernous sinus of otitic origin, Joseph G. Druss. ¶ Papers of the evening—a] The "blocked ear" of the caisson worker, Ralph Almour; b] Atypical facial neuralgia, George H. Hyslop. Discussion, Richard M. Brickner; c] Injuries of the larynx, traumatic and therapeutic, John D. Kernan. Discussion, Charles J. Imperatori.

MAY 17—*Section of Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, Lewis Clark Wagner; for Secretary, Joseph Buchman; for member of Advisory Committee, David M. Bosworth. ¶ Presentation of case. Loss of substance of the intervertebral disc following a spinal tap, John P. Stump. ¶ Papers of the evening—a] Posterior herniation of nucleus pulposus, Joseph S. Barr, Boston (by invitation). Discussion, Irving H. Pardee; b] Treatment of osteogenic sarcoma without early amputation, Albert Ferguson (by invitation). Discussion, Ralph E. Herendeen. ¶ General discussion.

MAY 20—*Section of Ophthalmology.* Executive session. Election of Section Officers and member of Advisory Committee—for Chairman, Algernon Reese; for Secretary, Brittain F. Payne; for member of Advisory Committee, David H. Webster. ¶ Presentation of single case reports—a] Necrosis of the cornea due to vitamin A deficiency, Herman K. Goldberg (by invitation); b] Traumatic retinal angiopathy, James W. Smith; c] Recurrent advanced carcinoma of the orbit and nose; electrocoagulation and plastic reconstruction, Tibor de Cholnoky; d] Streptothricosis of the lacrimal canaliculi, Alfred Johnston Elliot (by invitation); e] Congenital ptosis—Machek operation, Rudolf Aebli; f] Molluscum contagiosum of lid margin as a cause of follicular conjunctivitis, Phillips Thygeson; g] Traumatic cataract affecting anterior layer of congenital nucleus, G. Bonaccolto; h] Sarcoma of the choroid. Probing of the lacrimal canal with negative pole, Walter Hipp; j] Birth injury of cornea with "glass membrane" in anterior membrane, Charles A. Perera.

MAY 21—*Section of Medicine.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—for Chairman, Oswald R. Jones; for Secretary, Asa L. Lincoln; for member of Advisory Committee, Samuel W. Lambert, Jr. ¶ Presentation of cases—a] Subacute Streptococcus viridans end-arteritis complicating patent ductus arteriosus. Recovery following operation, Philip Rosen (by invitation). Discussion, Arthur S. W. Touroff; b] Hypercalcemia of undetermined origin, Hector Perrone (by invitation). Discussion, G. Jarvis Coffin; c] Hemorrhagic gastritis, Talcott Bates (by invitation). Discussion, Luis Amill (by invitation); d] Xanthomatosis resulting in coronary disease, Wilbur Downs (by invitation). Discus-

sion, John Dietrick (by invitation); e] Acute leukemia presenting a neurological picture at onset, George H. Stueck, Jr. (by invitation). Discussion, Joseph E. Connery; f] Recurrent bilateral pneumothorax with pneumonitis, Charles A. Ragan, Jr. (by invitation). Discussion, Norton S. Brown. ¶ General discussion.

Section of Genito-Urinary Surgery—The following were elected at the April meeting of the Section: Chairman, John H. Morrissey; Secretary, Frank C. Hamm; Member of Advisory Committee, John A. Taylor. There was no meeting of the Section in May due to the meeting of the Section of Urology of the Medical Society of the State of New York.

MAY 28—*Section of Obstetrics and Gynecology.* Executive session—a] Reading of the minutes; b] Election of Section Officers and members of Advisory Committee—for Chairman, Frank R. Smith; for Secretary, Harry Aranow; for members of Advisory Committee—(1) Alfred M. Hellman, (2) Edward H. Dennen, for one year (to fill the unexpired term of Francis W. Sovak, deceased). ¶ Presentation of cases. A case of endometrial sarcoma (Specimen—Microphotographs), Henry D. Furniss, C. L. Reid (by invitation). ¶ Papers of the evening—a] Practical consideration of chorioepithelioma, Louis J. Ladin. Discussion, Harvey B. Matthews, David N. Barrows, George Bolling Lee; b] A review of the maternity statistics of New York City for the year 1939, Mr. Thomas J. Duffield, Registrar of Records, New York Board of Health (by invitation).

AFFILIATED SOCIETIES

MAY 20—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Presentation of cases. ¶ Papers of the evening—a] The importance of field distribution measurement, Lillian E. Jacobson, M.A. (by invitation). Discussion, Myron M. Schwarzchild, M.A. (by invitation); b] Goldfish as a biological test object in roentgen therapy, F. P. Ellinger (by invitation). Discussion, Giacomo Failla, D.Sc. (by invitation); c] Roentgen therapy in leukemia; survival period and reaction of spleen and nodes, Lucien M. Pascucci (by invitation). Discussion, Ross Golden; d] Roentgen therapy of cancer of the lung; increase in survival period, William V. Tenzel (by invitation). Discussion, Harry Wessler (by invitation); e] Pulmonary and skeletal metastases from cancer of the kidney, prostate and bladder, Jacob R. Freid; f] Treatment of cancer of the ovary, James A. Corscaden (by invitation), Clara Okrainetz (by invitation). ¶ Executive session.

MAY 23—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case reports—a] A case of extragenital chorioepithelioma in the male, Houston W. Shaw (by invitation); b] A case of massive urolithiasis following massive heparin-sulfapyridine treatment, Arthur Schifrin. ¶ Papers of the evening—a] Experimental aspects of heparin-sulfapyridine in massive urolithiasis, William Antopol; b] Color photography at the autopsy table, with case illustrations, Jacob Werne, Hans Freivogel (by invitation), Charles Breedis (by invitation). ¶ Executive session.